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THE EFFECTS OF PROTAMINE INSULIN AND RELATED COMPOUNDS IN NORMAL AND DEPANCREATIZED DOGS.*

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Since the introduction of protamine insulin by Hagedorn, Jensen, Krarup and Wodstrup,[2] there have been many clinical confirmations of the findings of these authors. The observations to be presented here illustrate some of the characteristics of the action of protamine insulin, zinc insulin and protamine zinc insulin which are revealed by their use in normal and depancreatized dogs.

Methods. The protamine insulin used in the experiments to be described was very kindly supplied by the Connaught Laboratories of this University through the courtesy of Drs. D. A. Scott and A. M. Fisher. The protamine used was prepared from the testes of a species of Pacific salmon—"Onchorhynchus tschawytscha." The insulin was made up in a concentration of 40 units per cc. to which the protamine was added in the proportion of 0.8 mg. per 100 units of insulin. The amounts of zinc which were added to the insulin and to the protamine insulin will be described later.

Blood-sugar estimations were made upon venous blood by a modification of the Shaffer-Hartmann method. Sugar values were determined upon urine samples by diluting 1 cc. urine 200 times and making estimations upon 5 cc. aliquots by the modified Shaffer-Hartmann method.

Female dogs were depancreatized for use in these experiments by means of a one-stage operation under ether anesthesia. No experiment was carried out on these animals until at least 2 weeks after pancreatectomy. During

* A preliminary report of these results was presented by one of us (R. B. K.) at the Annual Meeting of the Society for Clinical Investigation, May, 1936, and published in the Journal of the Society (J. Clin. Invest., **15**, 450, 1936).

the period of experiment, the animals were fed a constant daily diet consisting of the following foods and divided into 2 or 3 feedings as indicated in the text; 400 gm. beef muscle (all visible fat removed), 200 gm. beef pancreas, 50 gm. cane sugar, 25 cc. tomato juice, 2 cc. cod-liver oil. To this diet in the later experiments 5 gm. of powdered yeast (Mead Johnson) were added.

Protamine Insulin in Normal Dogs. The effect of protamine insulin in various doses upon the fasting blood sugar of normal dogs illustrates very well the prolonged action of this compound. Experiments were carried out upon the same normal dog at intervals of not less than 5 days. During the time between experiments the animal was fed a diet of dog biscuits and meat scraps. On the day before an experiment, 17 to 18 hours prior to the injection of the insulin on the following morning, the dog was given a meal of lean beef and was then fasted until the end of the experiment. Water was provided *ad libitum*. The insulin was injected subcutaneously at or about 9.00 A.M. and blood sugars were determined at various intervals.

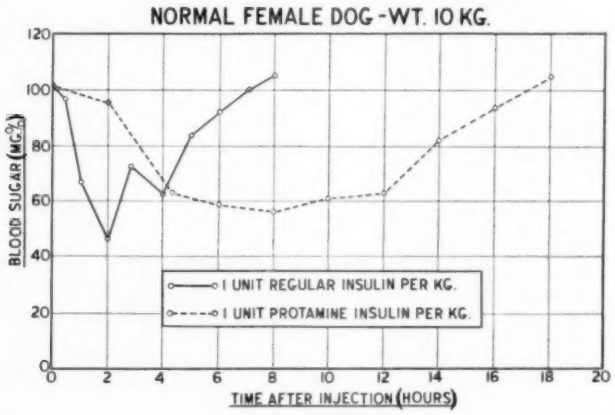

FIGURE 1

The results charted in Figure 1 illustrate the effect upon the blood sugar of a dose of 1 unit per kilogram of body weight of protamine insulin and of a similar dose of regular insulin. The effect of the regular insulin persists for about 6 hours whereas in the case of protamine insulin the blood sugar did not return to normal until 18 hours after injection. The difference in the rate of fall is also to be noted, that following protamine insulin being considerably slower than that produced by regular insulin.

In Figure 2 the results of various doses of protamine insulin upon the blood sugar of a normal fasting dog are shown. There is a marked difference in the amount of protamine and regular insulin which can be tolerated by a normal dog without demonstrating a hypoglycemic

reaction. In these experiments a dose of 2 units of regular insulin per kilogram of body weight produced convulsions whereas 4 units of the protamine preparation per kilogram was the smallest amount required to elicit a hypoglycemic reaction.

When hypoglycemic reactions occur following the administration of protamine insulin they usually appear many hours after the injection. In the experiments, the results of which are depicted in Figure 2, the reaction following the injection of 4 units of protamine insulin per kilogram did not take place until 28 hours after the insulin had been given.

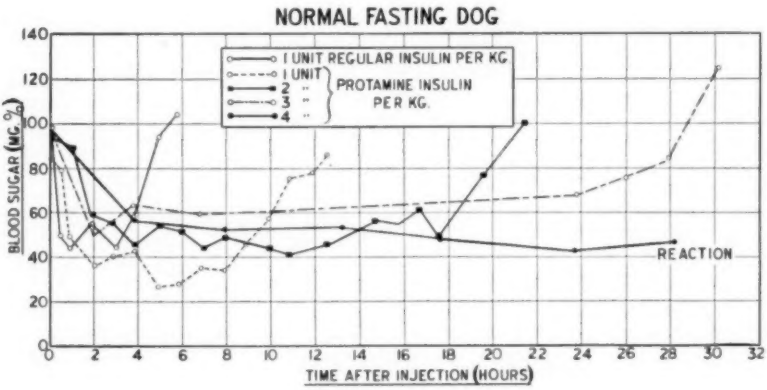

FIGURE 2

Up to a point the effect of increasing the dose of protamine insulin is seen to be that of prolongation of its action rather than a further depression of the blood sugar. It is extremely interesting that the blood sugar can be depressed for such long periods of time without the development of hypoglycemic reactions. In one experiment, it is to be noted that the blood sugar remained at a low level for 27 hours with no more evidence of hypoglycemia than a slight disinclination on the part of the animal to move about actively.

It has been noted in confirmation of the results of the Danish investigators that there is no appreciable difference between the effects of regular and protamine insulin upon the blood sugar when the insulin is administered intravenously.

Protamine Insulin in Depancreatized Dogs. The glycosuria and blood-sugar levels have been observed in depancreatized dogs receiving the two types of insulin.

Studies on Glycosuria in Depancreatized Dogs. Observations on 4 female depancreatized dogs were carried out to determine the extent of the glycosuria when the animals were receiving similar doses of regular or protamine insulin. The diet and amount of insulin were maintained at a constant level. The insulin was

injected subcutaneously daily at 9.00 A.M.; feedings were given at 10.00 A.M. and 4.00 P.M. The urine was collected in 24-hour specimens without catheterization.

Table 1 shows the results obtained from these experiments. The urinary sugar values represent the daily average for 7-day periods. The marked diminution in glycosuria when protamine insulin is being given is obvious.

Acetone appeared in traces in the urine during the period in which regular insulin was administered, but was absent during the period of treatment with protamine insulin.

TABLE 1.—GLYCOSURIA IN DEPANCREATIZED DOGS WITH REGULAR AND PROTAMINE INSULIN (ONE DOSE DAILY).

Dog.	Regular insulin.		Protamine insulin.	
	Dose of insulin (units) 9.00 A.M.).	Sugar excretion (gm.) (daily average 7 days.)	Dose of insulin (units) (9.00 A.M.).	Sugar excretion (gm.) (daily average 7 days).
"M"	17	40.9	17	1.0
"R"	26	13.2	26	1.7
"P"	34	56.1	34	5.6
"B"	30	48.3	30	2.7

Studies on Blood-sugar Levels in Depancreatized Dogs. One of the most dramatic effects of protamine insuiin is its ability to maintain a normal level of blood sugar in a depancreatized dog which is receiving only one dose of the preparation daily. This is quite impossible with regular insulin. The use of protamine insulin in this manner was suggested by the findings in normal dogs in which the blood sugar was found to remain at subnormal levels for 24 hours or longer after one injection of protamine insulin.

The results of one experiment are given in Figure 3. In this graph the blood-sugar levels of a depancreatized dog throughout a 24-hour period following one dose of regular insulin and a similar dose of protamine insulin are shown. The insulin was given at 9.00 A.M. followed by feedings at 9.30 or 10.00 A.M. and at 4.00 P.M. The periods depicted, in each case, followed after several days of similar treatment, so they are representative of the condition of an animal which had been stabilized on the particular routine employed.

The high fasting level of the blood sugar with regular insulin is to be noted. There is a rapid fall to a low value and subsequent return to a high level by the end of 24 hours. This demonstrates the rapid onset of action of regular insulin with failure to control the blood sugar for a period longer than 6 to 8 hours even with large doses. With protamine insulin a much more constant level of blood sugar is obtained. A low fasting blood sugar occurs in the morning, to be followed by a slight rise after the morning feeding. The afternoon feeding produces no effect upon the blood sugar and a normal fasting level is obtained on the following morning.

Similar experiments have been performed in which feedings have

been given at approximately the same intervals as adopted by human subjects. There were no essential differences in the results.

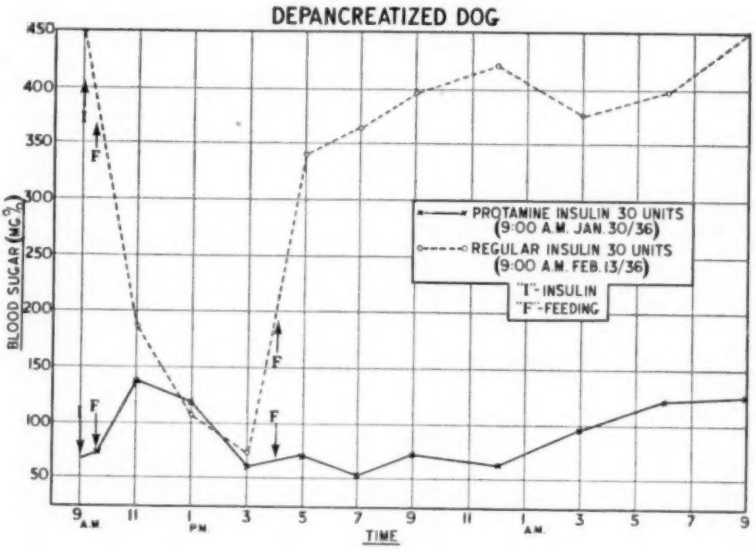

FIGURE 3

Zinc Insulin in Normal and Depancreatized Dogs. Scott and Fisher[3] reported that the addition of zinc salts to insulin prolonged the hypoglycemic effect of this hormone in rabbits. Their findings have been confirmed in normal and depancreatized dogs.

The zinc insulin used in these experiments was very kindly supplied by Scott and Fisher. It was prepared by the addition to regular insulin (40 units per cc.) of zinc chloride to make a concentration of 9 mg. zinc metal per 100 units.

Figure 4 represents a comparison of the hypoglycemic effect of regular and zinc insulin in a normal dog. The effect of the regular insulin is complete in 5 hours, while that of the insulin to which the zinc has been added continues for 19 hours. The onset of the depression of the blood sugar in the case of the zinc insulin is very slow compared to that of either regular or protamine insulin.

Figure 5 illustrates the results of experiments designed to compare the action of zinc insulin and regular insulin in a depancreatized dog. The blood sugar during the 24-hour period when one dose of regular insulin is given shows a marked "swinging" character, while that with zinc insulin is more constant. There is considerable rise during the period of feeding, but the blood sugar attains a normal value 24 hours later. The rise during the feedings is probably attributable to the slow onset of action of the zinc insulin.

Relation of Zinc to Protamine Insulin. In collaboration with Scott and Fisher and in extension of their work on rabbits, additional evidence of the importance of zinc in the protamine insulin compound has been secured. Preparations of insulin and protamine,

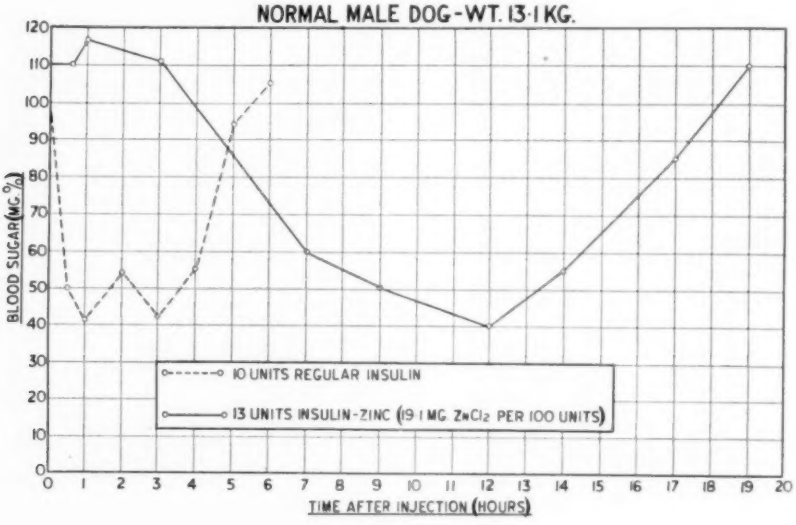
NORMAL MALE DOG - WT. 13·1 KG.
BLOOD SUGAR (MG. %)
TIME AFTER INJECTION (HOURS)
10 UNITS REGULAR INSULIN
13 UNITS INSULIN-ZINC (19·1 MG. ZnCl2 PER 100 UNITS)

FIGURE 4

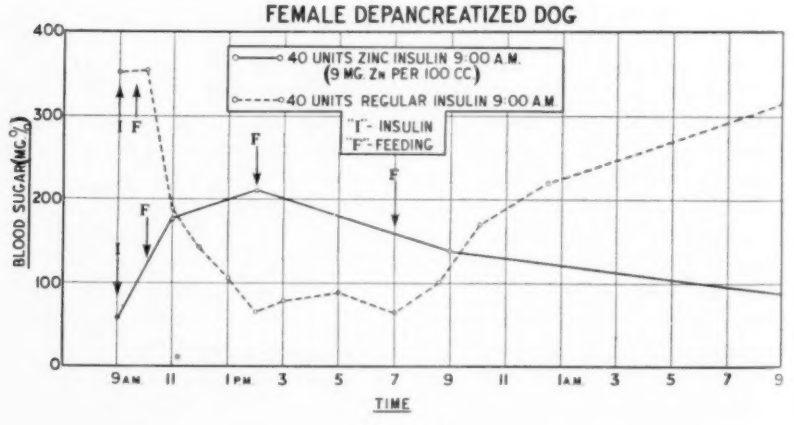
FEMALE DEPANCREATIZED DOG
40 UNITS ZINC INSULIN 9:00 A.M. (9 MG. Zn PER 100 CC.)
40 UNITS REGULAR INSULIN 9:00 A.M.
"I"- INSULIN
"F"- FEEDING
BLOOD SUGAR (MG. %)
TIME

FIGURE 5

made by these investigators by electrodialysis, were very nearly "ash-free." When these substances were combined in a buffered solution a precipitate was formed not unlike that produced upon combination of the cruder materials. However, upon injection into

normal dogs it was found that this "ash-free" compound did not possess the same ability to prolong the hypoglycemic action of insulin as did the cruder substances. The more prolonged effect was restored to the "ash-free" preparations by the addition of a very small amount of zinc chloride, in the proportion of 1 mg. per 500 units of insulin.

Figure 6 illustrates the results of one of these experiments. The first two curves show a comparison between the effects of regular insulin and regular insulin to which the small amount of zinc chloride has been added. The two curves to the right show the prolongation of action produced by the addition of the zinc chloride to the "ash-free" preparations. The mechanism of this action is not as yet clear, but it is probable that zinc or a related metal is responsible in some manner for the moderately stable linkage between insulin and protamine.

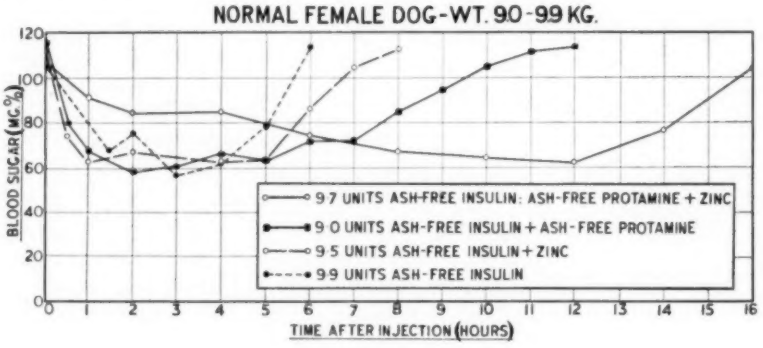
NORMAL FEMALE DOG-WT. 90-99 KG.
BLOOD SUGAR (MG.%)
TIME AFTER INJECTION (HOURS)
9.7 UNITS ASH-FREE INSULIN: ASH-FREE PROTAMINE + ZINC
9.0 UNITS ASH-FREE INSULIN + ASH-FREE PROTAMINE
9.5 UNITS ASH-FREE INSULIN + ZINC
9.9 UNITS ASH-FREE INSULIN

FIGURE 6

Experiments With Protamine Insulin Mixture With 15% "Free Insulin" Present. In a previous experiment it was noted that there was a marked difference in the rate of fall of the blood sugar following the administration of protamine and regular insulin. This no doubt accounts for the postprandial rise of the blood sugar after the morning meal, noted in the case of depancreatized dogs (Fig. 3) and in some clinical cases (Campbell, Fletcher and Kerr[1]).

It has been shown that protamine insulin usually contains little or no "free insulin" in the supernatant fluid after separation of the protamine-insulin precipitate. It is probable that the delayed fall of the blood sugar with protamine insulin is due to the slow liberation of insulin from the compound. If, however, some "free insulin" were available the slow onset of the action might be avoided.

Scott and Fisher have found that by reducing the amount of protamine in the mixture some of the insulin remains "free" and can be recovered from the supernatant fluid. Thus by using one-half the amount of protamine, *i. e.*, 0.4 mg. protamine per 100 units, some 15% of the insulin remains uncombined.

In Figure 7 the effect of this mixture upon the blood sugar of a normal dog is compared with that of regular insulin and protamine insulin containing the usual quantity of protamine (0.8 mg. per 100 units). All three preparations contained a small amount of zinc (1 mg. per 500 units). It is seen that the rate of fall of the blood sugar during the first few hours corresponds very closely in the case of regular insulin and the "free insulin" mixture. The onset of action of the protamine zinc insulin is slower than is usually the case. The length

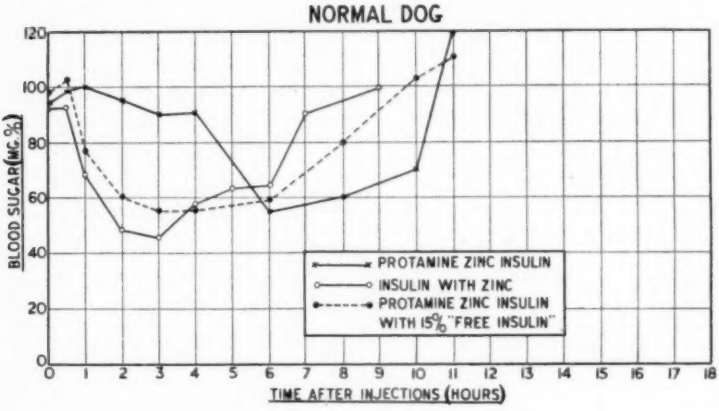

FIGURE 7

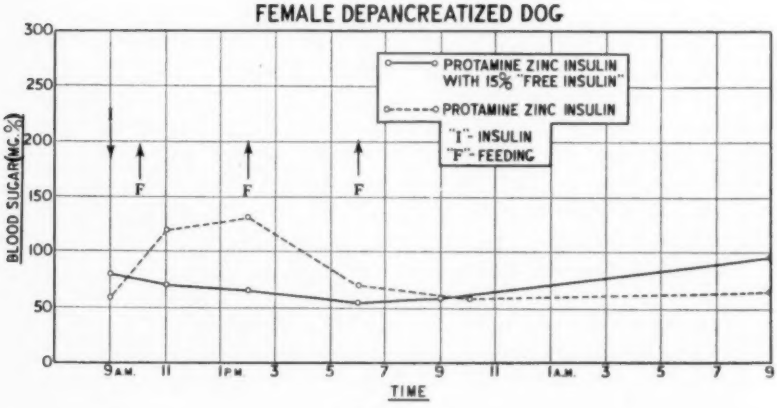

FIGURE 8

of action of the preparation containing the "free insulin" is slightly less than that of the standard protamine zinc insulin. There is considerable individual variation in the response of animals to these preparations.

In Figure 8 the ability of the preparation containing "free insulin" to prevent the postprandial rise of the blood sugar is demonstrated.

The results depicted here show a comparison of the effects of the two preparations of protamine zinc insulin upon the blood sugar of a depancreatized dog to which three feedings of a mixed diet have been given as indicated.

It is not yet possible, however, always to maintain a fixed amount of insulin free in the protamine insulin mixture. Variable results are therefore obtained. Some further work will be required before a preparation providing both free and combined insulin can be recommended for clinical trial. Further results of the use of this preparation in depancreatized dogs will be reported shortly.

Discussion. The response of the normal dog's blood sugar to an injection of protamine insulin reveals many points of interest. The long period of time during which the blood sugar is maintained at a fairly constant low level suggests that some mechanism such as the liberation of glucose by the liver is successfully combating the effect of the slowly released insulin. This effect may be produced by means of the secretion of adrenalin which is known to occur when the blood sugar reaches low levels.

The greater tolerance of the normal dog to protamine insulin than to regular insulin without the occurrence of hypoglycemic reactions is demonstrated in one of the experiments. It has been shown that an animal will remain in an apparently normal condition even though the blood sugar is depressed to levels which are usually regarded as productive of signs of hypoglycemia, such as incoördination, unconsciousness and even convulsions.

If it is postulated (1) that the signs of hypoglycemia are elicited when the sugar content of the fluid bathing cells of the central nervous system has been lowered to a certain level, and (2) that the lowering of blood sugar is due, in part, to utilization of sugar by the tissue cells generally, a rational explanation of the lower level of blood sugar at which the signs of hypoglycemia are observed with protamine as compared to regular insulin may be advanced. The sugar content of the tissue cells (and that of the fluid bathing them) will always be lower than the blood-sugar level. This discrepancy will be greater when sugar is being used rapidly under the influence of insulin which is quickly absorbed (*i. e.*, the blood sugar will be higher when the critical level of sugar in the cells of the central nervous system is reached) than when the tissue cells are stimulated less vigorously by insulin which is absorbed much more slowly. Under these latter conditions, when the concentration of the absorbed insulin in the blood and tissues is presumably lower than when regular insulin is used, the blood sugar will follow more closely the fall in tissue sugar and will, therefore, be lower when the critical level in the central nervous system is reached.

While fewer hypoglycemic reactions are observed in depancreatized dogs treated with protamine insulin than with regular insulin, the reaction produced by the slowly absorbed compound is

much more prolonged and much more difficult to alleviate. In 2 cases we have not been able successfully to combat the effects of hypoglycemia (which developed during the night and was therefore untreated for perhaps 8 to 10 hours) by the intravenous administration of dextrose. While the blood sugar was maintained at a high level by this treatment the animals continued to exhibit signs suggestive of a lesion of the central nervous system. They became progressively weaker and died about 48 hours after the first signs were noticed. While there is no doubt that the hypoglycemic reaction could have been completely alleviated if it had been promptly treated, it would appear that it is much more dangerous to postpone treatment of hypoglycemia resulting from the use of protamine insulin than that produced by regular insulin in comparable doses. When very large doses of regular insulin are used and the hypoglycemia is not treated for from 8 to 10 hours the situation is similar to that observed with protamine insulin.

Very little further comment on the effect of zinc insulin or of protamine zinc insulin in depancreatized dogs is required. It should be noticed that the contrast between the protamine insulin and protamine zinc insulin has been produced by the use of preparations of protamine and insulin in which the ash content has been greatly reduced. While some preparations of protamine insulin may contain such amounts of zinc or related metal that the addition of more metal is without pronounced effect on the duration of the antidiabetic action, this is frequently not the case. Protamine zinc insulin preparations are much more stable than the protamine insulin complex without added zinc (Scott and Fisher[3]).

The use of protamine insulin in depancreatized dogs has made possible experiments in which there is presumably a fairly regular liberation of insulin throughout the 24 hours. It is possible that further investigations on the action of insulin will be facilitated by the use of this compound.

Summary and Conclusions. The duration of effect of protamine insulin and regular insulin upon the blood sugar of depancreatized dogs has been compared. The rate of fall of the blood sugar with regular insulin is much greater than that with the protamine compound. The duration of the action of protamine insulin is much greater than that of regular insulin. The blood sugar of the normal dog may be maintained at a low level for much longer periods without production of the hypoglycemic reaction than is possible when regular insulin is used.

One dose of protamine insulin daily in depancreatized dogs is sufficient to keep the animal approximately sugar free. When the same amount of regular insulin is used in one dose there is a very heavy glycosuria.

The relatively steady level of blood sugar in depancreatized dogs with one dose of protamine insulin a day is in marked contrast with that observed when one dose of regular insulin is used.

Zinc insulin administered subcutaneously to dogs is apparently not readily absorbed but its action persists for prolonged periods. Additional evidence of the effect of zinc on the combination of protamine and insulin is presented (confirming Scott and Fisher).

The results of preliminary experiments, in which protamine zinc insulin mixtures containing some "free insulin" were used, are described. This preparation exerts a rapid effect which may also be almost as prolonged as that of similar mixtures which contain no "free insulin."

We are indebted to our colleagues, Dr. D. A. Scott and Dr. A. M. Fisher, for their kind coöperation. Some of the more recent experiments have been carried out with the help of Mr. E. A. Dobson.

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(1.) **Campbell, W. R., Fletcher, A. A.,** and **Kerr, R. B.**: Am. J. Med. Sci., **192**, 589, 1936. (2.) **Hagedorn, H. C., Jensen, B. N., Krarup, N. B.,** and **Wodstrup, I.**: J. Am. Med. Assn., **106**, 177, 1936. (3.) **Scott, D. A.,** and **Fisher, A. M.**: J. Pharm. and Exp. Therap., **55**, 206, 1935.

INVESTIGATION ON VOLUNTEERS INFECTED WITH THE INFLUENZA VIRUS.

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In order to determine the rôle played by the influenza virus in the etiology of epidemic influenza it is essential to study the infectivity of this virus for man under experimental conditions. If direct inoculation of the virus into human beings caused a disease which possessed the clinical, immunologic and epidemiologic characteristics of influenza a convincing argument in favor of the virus theory would have been presented.

The first attempts to infect man with the influenza virus were carried out by Andrewes, Smith and Laidlaw.[1] Two hospitalized volunteers were inoculated intranasally with 2 cc. of a filtrate of the respiratory tract washings from infected ferrets. Neither volunteer developed symptoms of influenza. Since blood sera obtained from the 2 patients, even before the attempted infection, contained neutralizing antibodies for the influenza virus, the negative results were regarded by the authors as being due perhaps to the insusceptibility of both volunteers to influenza. Other possi-

bilities considered to explain the failures were that ferret-passage may have attenuated the virus for man or that, as in the case of swine influenza, clinically characteristic human influenza may result only when the virus is accompanied by a second organism.

Experimental. During the period April to October, 1936, we conducted experiments in which human volunteers were inoculated either with the virus isolated during the last outbreak of influenza in Leningrad[2] or with the WS strain kindly sent to us from London by Andrewes, Laidlaw and Smith.

Materials and Technique of Inoculation. The total number of volunteers inoculated with the virus was 72. We also observed as a control group 12 persons inoculated with lung suspensions of normal mice. Forty-three of the volunteers were hospitalized for 15 to 20 days for clinical and laboratory investigation in the Therapeutic Clinic of the First Leningrad Medical Institute (Director, Prof. M. D. Tushinsky), and 29 in the contagious ward of the Central Military Hospital.

The method of inoculation was by inhalation of atomized suspensions, as in our previous investigation with Pfeiffer's bacillus.[3]

The material for inoculation in all experiments consisted in a 10% suspension of the lungs of white mice which had been infected intranasally with a lethal dose of the virus adapted to ferrets and mice. Mice furnishing virus were killed 2 days after inoculation. As our investigations have shown, the lungs at this stage are particularly rich in virus, 1 cc. of a 10% suspension containing 10^5 to 10^6 minimal lethal doses for mice. Only those lungs were selected for experimental purposes which on bacteriologic test showed no more than 5 saprophytic microörganisms to 1/20th part of the lung (*i. e.*, 100 bacteria in the entire lung). Some of the lungs (20 to 30%) were bacteriologically sterile. After careful trituration of the selected lungs with 10 volumes of physiologic saline in a mortar with sterile sand, 5 minutes' shaking with beads, and slight centrifuging, a homogeneous suspension was obtained for use in inoculation.

For inoculation by inhalation, the face of the volunteer was covered with a mask of the type used for ether-chloroform anesthesia, through the opening of which was passed the end of the outlet tube of a glass atomizer. In some of the later experiments, inoculation was carried out by means of a gas mask, the crimped tube of which was fastened to a small chamber in which the atomizing was effected. Into the glass atomizer were poured 10 to 15 cc. of the virus suspension. Air from an electric air-pump reduced the suspension into fine droplets which were introduced as a vapor into the mask, from which it was inhaled into the respiratory tracts of the volunteers. Inhalations were carried out for 15 to 60 minutes, during which each volunteer inhaled from 10^5 to 10^6 minimal lethal mouse doses of virus.

Symptoms Developing After Introduction of Influenza Virus Into the Respiratory Tract. Clinically, the most typical signs and symptoms shown by inoculated volunteers were as follows:

Hyperemia of the nasal mucosa and edema of the turbinates, lasting from 4 to 10 days, was observed in 40% of the volunteers. In certain cases this was accompanied by slight cyanosis with dilation of the capillaries. In about 20% of the inoculated persons considerable exudation of mucus from the nose was observed, beginning on the second or third day after inoculation and continuing for 3 to

10 days. At first the exudate was clear; then it gradually thickened, turning into a viscous mucus, but rarely of a purulent appearance. Sometimes symptoms of hyperemia and dryness of the nasal membranes with crusts predominated. Subjectively this was expressed by an increase in the sensation of dryness in the nose and throat and by difficulty of nasal respiration.

Three of the 72 volunteers suffered nosebleed. Hyperemia of the throat was noted in 28% of the cases, accompanied by a swelling of the tonsils, which in 2 cases developed into the signs and symptoms of follicular angina. In the larynx a slight hyperemia of the true vocal cords was occasionally observed, lasting from 1 to 5 days. The supra- and infra-orbital foramina were involved in 21 of the volunteers, as manifested by an irritation of the first and second branches of the trifacial nerve.

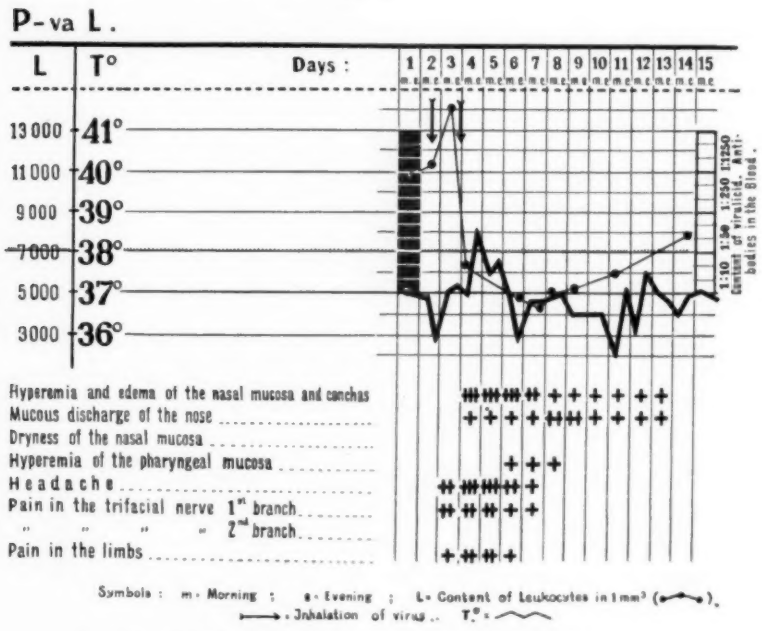
General symptoms, in response to inhalation of the virus, were observed in about one-third of the volunteers, while about one-fifth (14 cases) showed a whole series of clinical reactions identical with the most constant symptoms of epidemic influenza. Within 4 to 18 hours after inhalation the temperature rose to 37.5 to 39.0° C., with chills. The temperature reached its highest point within the first few days after inhalation and remained at this level, on the average, for 2 days. There was an acceleration of the pulse parallel to the rise in temperature. The experimental patients complained of headache, localized chiefly in the forehead, of rheumatic pains in the body and pains in the joints, cold in the head, or a congestion of the nose. In a portion of the patients we observed cough, pain upon moving the eyes, sleeplessness, liquid stool, and, in one instance, vomiting.

Abstracts of two representative cases follow:

Volunteer P. (Chart I), aged 18, admitted to the Clinic on May 5, 1936, showed no abnormalities in the internal organs or the upper respiratory tract. He was subjected on May 9 and 10 to repeated inhalations of the virus (2 inhalations of 15 minutes each). On May 11, 18 hours after the second inhalation, he had a severe chill. The temperature rose rapidly to 38.3° C. The patient complained of a severe headache in the region of the forehead, pain upon moving the eyes, rheumatic pains in the extremities and joints, cold in the head, and a slight, dry cough. He had a feverish appearance: red, shiny eyes and moist, reddish skin. The nasal mucosa contained a moderate quantity of clear mucus, and the throat showed slight hyperemia. The patient felt pain on pressing in the region of the supra-orbital fossa. Pulse 120. Heart and lungs normal; tongue moist and coated; abdomen soft and without pain. During the night of the 11th the patient was delirious; on the 12th his temperature fell to 37.8° C. There was profuse perspiration. On the third day of illness, a considerable improvement set in. The temperature fell to normal. The headache and cold in the head continued. The nasal mucosa showed pronounced hyperemia but there was no exudation from the nose. Within a few days the headache ceased, and an exudation of thick mucus from the nose developed, which continued during the rest of the patient's stay at the Clinic. The congestion and swelling of the nasal membranes gradually decreased. The hyperemia

of the throat disappeared 4 days after inhalation. A blood examination (Chart I) showed changes typical of epidemic influenza. The volunteer was discharged May 23.

CHART I.


P-va L.
L
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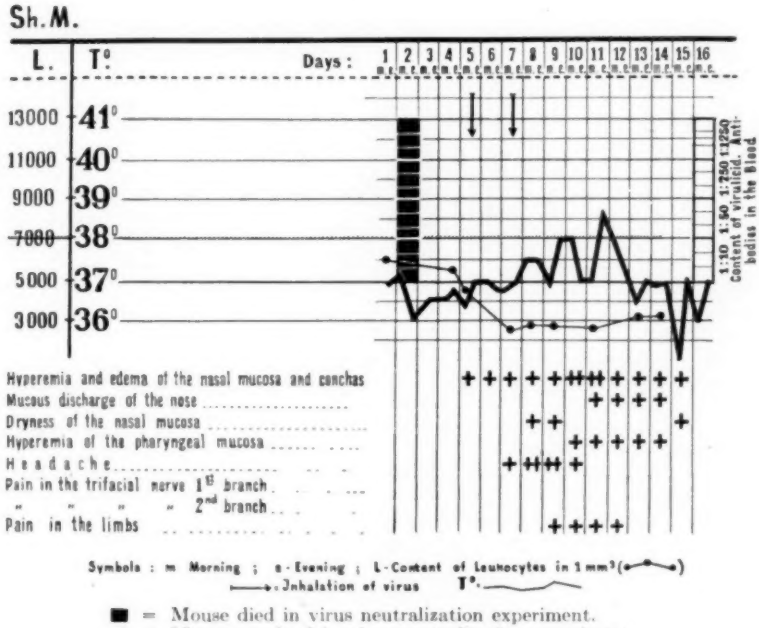
Days :
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
m e m e m e m e m e m e m e m e m e m e m e m e m e m e m e
13 000
11 000
9 000
7 000
5 000
3 000
41°
40°
39°
38°
37°
36°
1:10 1:50 1:250 1:1250
Content of virulicid. Anti-bodies in the Blood.
Hyperemia and edema of the nasal mucosa and conchas
Mucous discharge of the nose
Dryness of the nasal mucosa
Hyperemia of the pharyngeal mucosa
Headache
Pain in the trifacial nerve 1st branch
" " " " 2nd branch
Pain in the limbs
Symbols : m = Morning ; e = Evening ; L = Content of Leukocytes in 1 mm³ ( ).
= Inhalation of virus .. T.° =

■ = Mouse died in virus neutralization experiment.
□ = Mouse survived in virus neutralization experiment.

The second case presents complications of short duration. *Volunteer Sh. M.* (Chart II), admitted to the Clinic May 25, showed no abnormalities in the internal organs or upper respiratory tract, with the exception of a slight deformation of the nasal septum. The patient was subjected to two 30-minute inhalations of the influenza virus on the 29th and 31st. On June 1, the day after the second inhalation, she complained of a headache in the region of the forehead, congestion of the nose, and a slight, dry cough. Temperature 37.5° C., flushed face, intense hyperemia of the conjunctivæ and the nasal membranes, edema of the turbinates, and an accumulation of crusts in the lower nasal passages. Pulse 120, tone of the heart weakened. Respiration was difficult, with dry, whistling râles in the left lung under the angle of the scapula. There was no abdominal pain. On June 2 the patient felt worse. She complained of pronounced weakness and rheumatic pains throughout the body. Temperature increased to 37.6° C. Sputum was expectorated. Symptoms in the upper respiratory tract remained the same. The left lung under the angle of the scapula revealed a small section with moist and dry râles. Stool was retarded. On the 3d, shooting pains under the left scapula and increased coughing were noted. Temperature was 38.6° C. Hyperemia of the nose was more pronounced; edema of the turbinates continued, but with no exudation. In the lungs to the left under the scapula there was a shortening of the percussion tone, with a strengthening of bronchophony. Auscultation revealed moist and crepitant râles at the height of inhalation. On the 4th, general weakness, prostration

and an intensification of the head cold were observed. Temperature was 38.0° C. Hyperemia of the nose and edema of the turbinates were without change, but a small amount of thick mucus appeared. Membranes of the throat showed slight congestion and moistness. During the next few days the temperature fell to normal. The symptoms in the upper respiratory tract and lungs gradually disappeared. When discharged, the patient showed considerable exacerbation of the pain in the joints. Blood examination indicated a distinct leukopenia coupled with a considerable increase in specific virus-neutralizing antibodies.

CHART II.



The 12 persons in the control group, inoculated with suspensions of lungs from normal mice, exhibited no evidence of illness and remained clinically normal throughout the period of observation.

The Blood Picture During Experimental Virus Influenza. White blood cell counts of all volunteers were taken 2 to 3 times before inoculation and 5 to 9 times during the course of the first few days after inhalation.

Of the 72 volunteers, 25 (34%) reacted to inhalation with a decrease in the white cell count to less than 6000 per c.mm. One-third of this group showed leukocytosis for one day, changing during the subsequent days to leukopenia. Leukopenia generally developed on the first to the fourth day after the first inhalation and continued for 3 to 5 days. In a considerable number of cases the intensity of

leukopenia was parallel with the development of the objective and subjective symptoms of illness. Only rarely was leukopenia the sole symptom pointing to an interaction between the virus and the human organism. Usually it was accompanied by other clinical manifestations. It should be emphasized that, in those patients showing distinct leukopenia, an especially pronounced increase in specific virus-neutralizing antibodies was observed. The white cell picture of volunteers with leukopenia was characterized (in absolute values) by neutropenia, lymphopenia, eosinopenia and monocytosis.

Thus the blood picture of many of the persons inoculated with the influenza virus conformed exactly with that described for epidemic influenza (Rütimeyer, Naegeli).

From the data of one of us (A.A.K.) obtained during the 1936 epidemic in Leningrad, leukopenia was a most constant finding in uncomplicated epidemic influenza. It was observed particularly often on the second or third day of illness, when it was extremely pronounced (up to 3000 per c.mm.). In approximately 20% of the patients with uncomplicated epidemic influenza leukopenia was preceded by leukocytosis lasting for one day. After the fourth day of illness the leukopenia became less distinct, and on the 10th or 11th day the leukocyte count returned to normal. The leukocytic picture of uncomplicated epidemic influenza showed the following changes:

1. Lymphopenia on the first 2 days of illness, disappearing by the 5th day and changing during the next few days into a pronounced lymphocytosis.
2. Neutropenia, most distinct by the 5th day of illness, and returning to normal in 8 to 12 days.
3. Eosinopenia, or a complete disappearance of eosinophils.
4. Monocytosis in a considerable number of patients, especially during the first 2 days. The monocytes in the majority of cases were atypical and in structure of the nucleus and protoplasm resembled histiocytes.

Minor differences between the blood pictures of experimentally infected volunteers and naturally-occurring cases of influenza consisted mainly in a less extreme leukopenia and an absence of toxic and degenerative alterations in the neutrophils in the experimental cases.

In the cases of 12 of the 72 volunteers the white cell count increased after inhalation of the virus. All volunteers of this group either had infective foci before inhalation (chronic inflammation of the accessory sinuses of the nose, chronic purulent otitis, abscesses on the fingers, etc.) or suffered some other complication after inoculation (angina, pneumonia, localized bronchitis, gumboil, etc.).

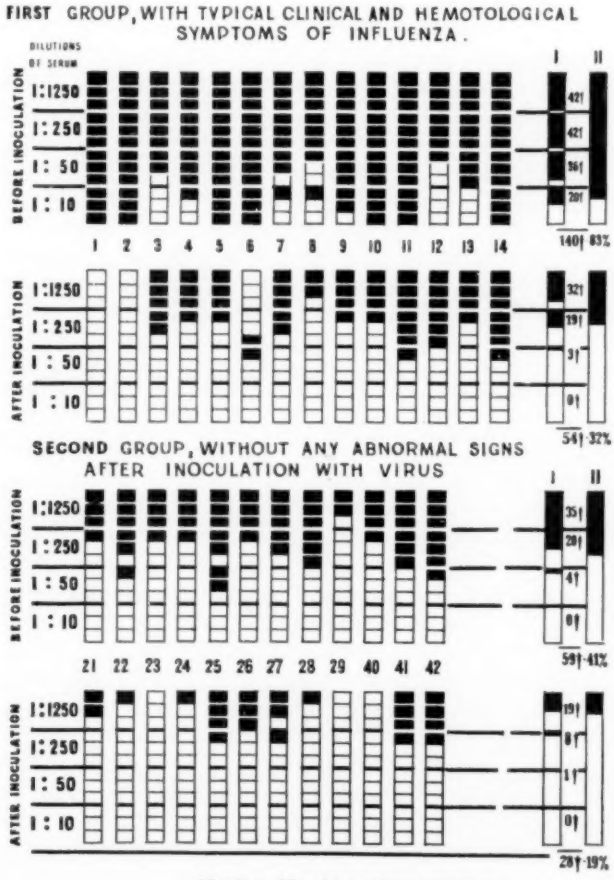
In the remaining 35 volunteers inhalation of the virus had no noticeable effect on the leukocyte count.

Immunologic Changes in the Blood of Inoculated Volunteers. *Method for the Quantitative Titration of Protective Antibodies.* In the majority of cases blood was drawn both before inoculation, and again 10 to 15 days after inoculation, from each volunteer. Titrations of the virus-neutralizing

antibody content of both serum samples from each patient were conducted simultaneously. Samples of various dilutions of the serum were mixed with equal amounts of a suspension of the Leningrad virus. The final dilutions of the serum were 1 in 10, 1 in 50, 1 in 250 and 1 in 1250. The quantity of virus used was 0.05 cc. of a 1 in 400 dilution, corresponding to 100 to 250 MLD for mice. After 30 minutes' contact at room temperature each serum-virus mixture was introduced intranasally into 3 mice under ether anesthesia. All the mice succumbing after 5 to 10 days were autopsied, and death was considered due to virus infection only in those cases in which the lungs showed complete hepatization and contained but few bacteria.

CHART III.

CONTENT OF VIRULICIDAL ANTIBODIES IN THE BLOOD OF HUMAN VOLUNTEERS.


FIRST GROUP, WITH TYPICAL CLINICAL AND HEMOTOLOGICAL SYMPTOMS OF INFLUENZA.
DILUTIONS OF SERUM
BEFORE INOCULATION
AFTER INOCULATION
1:1250
1:250
1:50
1:10
1 2 3 4 5 6 7 8 9 10 11 12 13 14
I II
42% 42% 36% 20%
140 83%
32% 19% 3% 0%
54 32%
SECOND GROUP, WITHOUT ANY ABNORMAL SIGNS AFTER INOCULATION WITH VIRUS
35% 29% 4% 0%
59 41%
21 22 23 24 25 26 27 28 29 40 41 42
19% 8% 1% 0%
28 19%
Absolute No. for various dilutions
Mortality of mice
Total per cent
= Mouse died in virus neutralization experiment.
= Mouse survived in virus neutralization experiment.

The results of the investigation are given in Chart III. The virus-neutralizing antibody content of each serum is represented in the form of columns consisting of 12 squares divided into 4 groups, depending upon the dilution of the serum. Each black square represents the death of a mouse, and each white square its survival. The data in the upper portion of the table (First group) was derived from 14 volunteers who developed clinically typical influenza with leukopenia following inoculation with influenza virus. The data in the lower portion of the table (Second group) represents the findings in the cases of 12 volunteers who exhibited no clinical evidence of influenzal infection as a result of inoculation with the virus.

The results of the immunologic study indicate, first of all, that the development of the experimental disease by inoculated volunteers is closely dependent upon the quantity of specific antibodies in their blood before inoculation. Thus, in the group which showed distinct symptoms of influenza following inoculation, the concentration of protective antibodies in the blood before inoculation was extremely low; in a considerable number of these even the lowest dilution of serum failed to neutralize 100 lethal mouse doses of virus. On the other hand, the blood sera of the majority of the volunteers in the second group, who proved resistant to large doses of the mouse virus, showed a high content of specific antibodies even before inoculation. Serum dilutions of 1 in 10 in all cases, and dilutions of 1 in 50 in a majority of cases (and some dilutions of 1 in 250) neutralized the dose of virus employed in the mouse protection tests.

To summarize the neutralization experiments with sera obtained from volunteers prior to inoculation, 146 of 168 mice (87%) receiving mixtures of virus and sera from susceptible persons (First group) died, while of 144 mice injected with virus and sera from non-susceptible volunteers only 59 (41%) died.

A second fact, clearly shown by the data in Chart III, was that the virus-neutralizing antibody content of the sera of the majority of the volunteers was markedly increased following inoculation with influenza virus. This was especially true in the first group, showing clinical symptoms, and here 25 to 100-fold increases in the antibody titer were usual. In isolated cases (Nos. 1, 2, 4) the quantity of antibodies after 2 or 3 inhalations of the virus reached exceptionally high values: a serum dilution of 1 in 1250 still neutralizing 100 MLD for mice of the virus. A distinct and consistent increase in the neutralizing antibodies in the sera of volunteers of the second group (resistant) after inoculation with influenza virus was also observed, though here the increase was less pronounced than that found in the first group. It is probable that in immune individuals the virus is too rapidly destroyed upon introduction into the respiratory tract to elicit a maximal immunity response.

These data permit one to conclude that inhalation of influenza virus, attenuated by protracted passage through ferrets and mice,

may be worthy of attention as a means of increasing the quantity of protective antibodies in human beings and perhaps also of enhancing their resistance to a subsequent influenza infection. We are now accumulating information on the duration and intensity of the specific alterations in the blood of those subjected to inoculation, as well as developing methods for the active immunization of humans by means of inhalation of the virus.

We should like to emphasize that the results of these immunologic studies obtained in human volunteers experimentally infected with the passaged influenza virus conform completely with the observations on uncomplicated influenza made during the time of the recent outbreak in Leningrad (1936). At that time we determined that there was a regular and sharp increase in the concentration of specific antibodies in the blood of influenza convalescents. We demonstrated that, while the majority of investigated sera obtained from influenza patients during the acute stage of their disease failed to neutralize virus even in 1 in 10 dilutions, the sera of patients after convalescence were active in dilutions of 1 in 250 and in rare cases even in dilutions of 1 in 1000. In other words, the concentration of influenza virus-neutralizing antibodies was increased 25 to 100-fold following an attack of influenza.

Fate of the Inhaled Virus. The period of time during which influenza virus persists on the upper respiratory tract mucosa of inoculated volunteers has been studied. In these experiments throat washings, obtained from volunteers at various intervals after inhalation, were tested for virus by mouse inoculation.

Method. Various dilutions of the throat washings (1 to 1, 1 to 10, etc. to 1 to 100,000) were introduced intranasally into white mice, three mice being used to test each dilution. After 6 days the mice which survived were killed and a 10% suspension of their lungs was used for the inoculation of fresh mice. If the latter died of virus infection, it was concluded that the virus was present in the given dilution. The results of one of the experiments in this series are given in Table 1.

TABLE 1.—DILUTIONS OF THE THROAT WASHINGS OF 3 VOLUNTEERS INOCULATED BY A 30-MINUTE INHALATION OF THE VIRUS.

	1:1	10^{-1}	10^{-2}	10^{-3}	10^{-4}	10^{-5}
Immediately after inoculation	+	+	+	+	+	−
After 4 hours	+	+	+	−	−	−
After 24 hours	+	+	−	−	−	−
After 48 hours	+	+	−	−	−	−
After 72 hours	−	−	−	−	−	−

+ = Influenza virus present. − = Influenza virus absent.

As shown in the table, the rather high concentration of virus immediately after inoculation diminished markedly within 24 to 48 hours. It seems highly probable that the virus used to inoculate the volunteers had lost much of its original virulence for man as a result of its repeated passage through ferrets and mice.

This rapid disappearance of the virus from the inoculated volun-

teers definitely agreed with the data of the immunologic studies upon the experimental cases. The higher the content of specific antibodies in the blood before inoculation the more rapid was the disappearance of the introduced virus. And, inversely, the longest persistence of the virus was observed in those volunteers having a low level of protective antibodies.

The low virulence of the passaged strain of the influenza virus may also account for the failure of the experimental disease to spread by contact to the surrounding personnel. This point, however, requires additional confirmation through observations on people more fully susceptible to influenza, inasmuch as the present investigation was carried out immediately after the end of the 1936 epidemic in Leningrad.

The Effect of Inhalation of the Virus on the Bacterial Flora of the Throat. Bacteriologic investigations carried out on patients with uncomplicated epidemic influenza at the time of the last outbreak in Leningrad disclosed large numbers of pneumococci, Pfeiffer's bacilli, catarrhal micrococci, and in many cases, also hemolytic streptococci in the throats of 32 patients during the first few days of illness. The highest concentration of these bacterial invaders was reached in the first 5 to 6 days. After convalescence (10 to 15 days after the onset of the disease) the average number of these microörganisms fell to a value one-thousandth or less of that observed during the first few days of illness. This suggested that the primary infective agent in epidemic influenza—probably a filtrable virus—lowers the resistance of the respiratory tract to such an extent as to permit the widespread multiplication of bacteria like the pneumococcus or Pfeiffer's bacillus. In consequence, there may be formed in the nose and throat a great reservoir of infective organisms, which play a decisive rôle in the development of the various complications of influenza.

It seemed of considerable interest to determine whether such an activation of the secondary microörganisms took place in the cases of human beings experimentally inoculated with the virus. Repeated bacteriologic examinations of 48 volunteers before inoculation and on various days after inhalation of the virus, however, failed to reveal any quantitative or qualitative changes in the bacterial flora of the upper respiratory tract in response to the introduction of the virus. Even in the volunteers who reacted to inhalation with a whole series of symptoms very similar clinically to naturally-occurring influenza did we fail to observe a distinct activation of pneumococci, hemolytic streptococci, Pfeiffer's bacilli or catarrhal micrococci. This was true even in the cases in which these bacteria were present before inoculation. The failure to note distinct activation of the bacterial flora of the upper respiratory tract in the infected volunteers may have been due either to the quality of the virus used in inducing the infections (passage of the virus in animals may have attenuated it for man) or to the low virulence of the

bacteria naturally vegetating in the upper respiratory tracts of most healthy people.

On the basis of our experiments, we may conclude that the inhalation of large doses of influenza virus is relatively harmless since our volunteers showed either no distinct reactions or symptoms of only a mild influenza. These findings make it highly worthwhile to study further the possibilities of the use of inhaled influenza virus as a means of actively immunizing people against epidemic influenza.

Summary. 1. About 20% of the 72 volunteers to whom large doses of the Leningrad virus or the WS virus of Smith, Andrewes and Laidlaw were administered by inhalation showed a series of clinical and hematologic changes conforming with the main findings in mild influenza. Considering the fact that only some of the volunteers became ill and these with but a light form of influenza, it is evident that the inhalation even of large doses of the virus previously adapted to ferrets and mice is relatively harmless for humans.

2. The development of the experimental illness was found to be closely related to the quantity of specific protective antibodies contained in the blood of the volunteers inoculated with the virus. All cases showing clinical symptoms typical of influenza had a low value of virucidal substances before inoculation. The majority of volunteers not reacting to the introduction of the virus showed large quantities of specific antibodies even before inhalation.

3. A considerable number of the inoculated individuals reacted to inhalation of the virus with an increase in the quantity of neutralizing antibodies in the blood. An especially large increase in the concentration of these virucidal substances (25 to 100 times) was noted in those volunteers showing the clinical symptoms of influenza. It is evident from this that inhalation by humans of the virus attenuated by passage through ferrets and mice, is worthy of study as a method for decreasing the susceptibility of people to influenza infection.*

4. Virus which has been adapted to the ferret and the mouse appears to have lost thereby its original virulence for man and to be incapable of further multiplication in the human organism. This was indicated by our observation that the influenza virus, introduced into the individual in the form of a suspension of the lungs of diseased mice, did not multiply in the mucosa of the respiratory tract

* The suggestion that influenza virus be administered by inhalation as a prophylactic measure against epidemic influenza seems, for the present at least, a heroic recommendation. Our knowledge concerning the properties and activities of the virus is as yet incomplete, we know nothing concerning its possible fluctuations in virulence, and the complications to which it may give rise are unpredictable. Influenza is a notoriously variable and protean disease and until we have some understanding of why, even in a given epidemic, it may manifest itself as an extremely mild illness in one individual and a rapidly deadly ailment in another, any method of immunization dependent upon actual infection, even with an apparently attenuated strain of virus, must be viewed yet as purely an experimental procedure and not applicable to widespread and general use.—EDITOR.

and died off during the course of the first few hours after inoculation. It was also shown that an activation of the potentially pathogenic microörganisms (Pfeiffer's bacillus, the pneumococcus, and the hemolytic streptococcus), so common in cases of genuine epidemic influenza, did not occur in individuals inoculated by inhalation with large doses of the animal-passaged influenza virus.

We are deeply indebted to Dr. Richard E. Shope for his interest in our work and his kind assistance in revising the manuscript.

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VALUE OF FEVER THERAPY IN THE ARTHRITIDES.*

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Since the foundation, in November, 1934, of the University of Nebraska Fever Therapy Research Department, now located at the Bishop Clarkson Memorial Hospital in Omaha, we have treated 172 arthritic patients, of whom this report covers 81 cases. This department uses for the induction and maintenance of fever three Kettering hyperthermst operated by a corps of specially trained nurses.

Each patient is carefully examined before treatment to determine eligibility and tolerance for fever therapy, one requisite being that the patient must be a good surgical risk before submitting him to the high fever, 106 to 107° F., necessary in the treatment of gonorrheal arthritis. The lower fevers, 103 to 104.5° F., used in the treatment of the other forms of arthritis, fortunately do not require such strict limitations. A careful history, complete physical examination with special emphasis upon locating focal infections, Roentgen rays of the sinuses, and of at least one of the affected joints, blood Wassermann test, blood sedimentation rate, complete blood count, and urinalysis are done on each case in order properly to diagnose and classify the type of arthritis.

All cases are under the supervision of an Arthritis Committee‡ which consists of four internists, an oto-laryngologist, an ortho-

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† We are indebted to Dr. Charles F. Kettering, Director of General Motors Research Department, and Dr. Walter M. Simpson, Director of the Kettering Institute for Medical Research, Miami Valley Hospital, Dayton, Ohio, for the loan of the Kettering Hyperthermes used in our studies.

‡ F. Lowell Dunn, M.D., Chairman; Lynn T. Hall, M.D., F. W. Niehaus, M.D., and E. E. Simmons, M.D., Internists; Delbert K. Judd, M.D., Oto-laryngologist; Herman F. Johnson, M.D., Orthopedist; F. Lowell Dunn, M.D., Clinical Pathologist.

pedist, a roentgenologist, and a clinical pathologist. Various members of this committee carefully study each case and utilize all rational types of therapy for the various arthritides, but are primarily interested in evaluating the rôle of fever therapy in these diseases.

Acute Rheumatic Fever. The excellent results obtained by fever therapy in the treatment of chorea interested us to try the same treatment in that most serious and incapacitating illness of the acute rheumatic fever triad, namely, acute rheumatic endocarditis; and to study our chorea patients carefully for evidence of complicating rheumatic endocarditis.

To date we have treated 9 cases of acute rheumatic fever with endocarditis and have also observed the results of fever therapy in 3 cases of chorea, which started primarily as rheumatic endocarditis, later developing typical chorea. The duration of the active state of acute rheumatic fever in these 12 cases ranged from 1 week to 9 months. All had active rheumatic endocarditis, with clinical findings of valvular heart disease, fever, and laboratory evidence of activity, and 1 had complicating rheumatic pericarditis. The patients' ages ranged from 7 to 40 years.

The treatment of cases of acute rheumatic fever consists of maintaining a fever of 103 to 105° F., depending on the response of the patient, for a period of 2½ to 4 hours. We feel that prolonged treatments of higher fevers are not well tolerated by these cases. The treatments are repeated every 3 or 4 days until the disease is improved or becomes inactive.

Following is the report of a typical case with a good result:

Case 1.—A woman of 40 had rheumatic pains, low-grade fever, marked mitral stenosis in an active stage of endocarditis; and 6 weeks of almost total bed rest, large doses of salicylates, and supportive treatment had failed to improve or relieve fully the pain. She withstood the fever treatments very well, with no apparent heart embarrassment. After 5 treatments her pain was gone, she was free of fever, her leukocyte count was normal, and her sedimentation rate was much lower. She left the hospital at the end of 22 days.

Five similar patients with acute articular rheumatism and active rheumatic endocarditis, after an average of 5 fever treatments, became free of pain and fever and had laboratory findings indicative of a prompt return to the inactive stage of acute rheumatic fever. One of these patients had acute rheumatic pericarditis which, after becoming steadily worse under bed rest and large doses of salicylates, cleared up following 4 fever treatments. He left the hospital 20 days after admission.

The 3 following cases showed moderate improvement but less favorable results than the preceding 6.

Case 1.—A man, with slight active endocarditis and severe pains previously requiring opiates, left the hospital after two fever treatments with some remaining pains, but free of fever, with normal leukocyte count and

much slower sedimentation rate. When heard from a month later he was entirely free of pain and fever and in good health. His slight pain on dismissal and a tonsillectomy which made it impossible to evaluate the results from the fever therapy classify him in the list of less successful cases.

CASE 2.—A girl of 11 was seen 1 week after an acute exacerbation of acute rheumatic fever, with a moderate degree of mitral stenosis, a fever and rather intense joint pains and became after 3 fever treatments free from pain and fever, with normal laboratory findings. She remained free of symptoms for 2 months and then had a recurrence of fever, acute endocarditis and rheumatic nodules, which required 4 months of bed rest to clear up. Although she responded well to fever therapy, her early relapse proved disappointing. Her case may well have deserved more treatments.

CASE 3.—A girl of 18 with very painful joints, low-grade fever, systolic murmur over apex transmitted to axilla, and incapacitated for 9 months, after 9 fever treatments was improved enough to return to school this fall. She has had moderate relief, more than with any other type of treatment, but not an entire relief of symptoms. A longer subsequent period is necessary in order fairly to evaluate her treatment.

In our group of chorea patients we found 3 cases which had started as acute articular rheumatism with endocarditis, later developing chorea. These patients ran low-grade fever and had the laboratory and auscultatory heart findings of active rheumatic endocarditis. Their ages ranged from 9 to 10 years, and the duration of the disease ranged from 2 weeks to 4 months. All of these patients, following an average of 9 fever treatments, became free of choreic manifestations, fever and pain; and their laboratory findings indicated that they were in an inactive stage of rheumatic fever. One has remained for over 1 year in excellent health and free of all evidence of active rheumatic disease, including the heart murmur.

Thus, in 9 cases of acute rheumatic fever with endocarditis, 6 became inactive in a relatively short period, an average of 24 days. The 3 cases of chorea with rheumatic carditis observed became inactive in an average time of 46 days; this longer period was due to treatments, in the beginning of our work, spaced at only weekly intervals. In the series, 75% have become inactive, free from pain and fever after an average of 7 fever treatments. In the remaining 25%, it is possible that additional treatments would have produced more favorable results.

Because of the small number of patients who have come under our observation and the short time that has elapsed since treatment, we cannot form definite conclusions. In rheumatic fever it is especially hard to determine what effect artificial fever has on the great tendency for relapses of activity to occur. We hope in the future to determine whether this type of therapy will prevent such recurrences of activity. But even though some patients may continue to have relapses after artificial fever therapy, we believe it possible, by shortening the duration of each period of activity, to reduce to a minimum the damage to the heart.

In consulting the literature we find reports[6,11a] on results of artificial fever therapy produced by various vaccines, serums and

foreign proteins in treatment of acute articular rheumatism—with apparently good results. We can find only two reports on the results of artificial fever therapy, mechanically produced, in the treatment of acute rheumatic fever with endocarditis *per se*,[11b,c] but there are numerous reports on the results in the treatment of chorea.[3,7,9] Some of these authors comment on the fact that chorea patients with endocarditis tolerate the treatments very well, and that there is no apparent heart damage from fever therapy. Some state that they believe the rheumatic and endocarditic phase may be slightly benefited,[8] but this feature of the disease, for the most part, has only been casually observed, because observers were primarily interested in the outcome of the chorea. Barnacle, Ewalt and Ebaugh[1] report 13 cases of chorea, 8 of whom had a complicating rheumatic endocarditis. An analysis of their report definitely shows that the rheumatic endocarditis was improved in 6 of the 8 cases.

Conclusion. When we take into consideration the chronic nature of rheumatic fever, the serious heart complications, the lack of any recognized therapy other than prolonged bed rest, supportive measures, and climatic changes, we believe that artificial fever therapy provides sufficient promise to justify further trial. The results obtained in chorea, one phase of this disease, justify this attitude. We feel from our limited observations that the marked relief seen in such a short period of time in 75% of our cases is a great improvement over any other type of therapy now used, and should encourage others to try this type of treatment and report their results.

Gonorrheal Arthritis. Out of 32 cases of gonorrheal arthritis treated in our fever therapy department, we have selected 23 with adequate diagnostic and follow up work from which to draw conclusions. There were 15 males and 8 females, with ages ranging from 19 to 50; the duration of the disease was from 4 days to 1 year.

The fever treatment in these cases consisted of 6 hours of fever of 106 to 107° F., repeated every 3 to 5 days, according to physical condition of the patient; the usual maximum was 25 hours.

Of these 23 cases, 15 (65%) were cured during the time they received treatments. We classify as cured those cases in which there was a complete cessation of pain and an absence of evidence of active inflammation, though not necessarily a complete return to normal function in the affected joints. Several with complete or almost complete ankylosis had only a great improvement of movement in the affected joints, with 50 to 75% of normal range at the end of treatment. Of the 15 cured cases, all of whom had other manifestations of gonorrheal infection, it was possible after fever therapy to get positive urethral smears in only 2. These 2 cases were entirely pain free and had no other evidence, subjective or objective, of their gonorrheal arthritis. There were 4 cases (17%) with marked improvement. Although these patients were greatly

improved, they still had a little pain on motion or a slight degree of swelling in the affected joints. Three cases (13%) received only slight improvement from their treatments. Only 1 case (4%) received practically no benefit, easily attributable to insufficient treatment.

The cases that were cured received an average of 25 hours of fever between 106 and 107° F., those markedly improved received an average of 27.8 hours, the cases with slight improvement received only 8.5 hours, and the unimproved case only 7 hours of this same elevation of fever.

In examining our records, contrary to the experience of others,[5,10] we were unable to determine any factors that might indicate the type of result to anticipate, with the exception of those cases having exostosis of the os calcis. The duration of the disease in the cured group ranged from 4 days to 7 months, in the markedly improved group from 4 days to 6 months, in the slightly improved group from 2 weeks to 1 year, and in the unimproved case the disease was of only 4 days' duration. There were no definite clinical or laboratory findings that were of benefit in prognosticating the end result other than the cases with spurs of the heel (os calcis), which required more hours of sustained fever to become pain free.

Apparently the only criteria for cure of this type of arthritis are the subjective and objective findings in the affected joints, disregarding positive smears for the gonococcus. Most of the treated cases continued to improve for some weeks after the termination of fever therapy.

Thus, 82% of the cases treated were either cured or markedly improved; the other 18% did not receive enough fever therapy to be of value.

An analysis of all of these findings would indicate that our slightly improved cases and the unimproved case received insufficient fever therapy to get a good result. It would seem that a minimum of 25 hours of fever between 106 and 107° F., the average amount of fever in cured cases, is necessary before drawing adverse conclusions in the individual case. Indeed, when a case difficult to classify is seen, and the patient does not show marked benefit from fever therapy, a more careful examination often discloses that we are dealing with chronic infectious arthritis that also has a focus of gonococcal infection.

Our experience has also shown us that the cases with rather severe deformities require adequate orthopedic measures as well as fever therapy.

Conclusion. It is our belief that artificial fever therapy is the best treatment now available for gonorrheal arthritis. Most patients, unable to move on account of severe pain, are practically free of pain after one session of fever. The greatest advantage is probably the rapidity with which a favorable result is obtained, thus

greatly shortening a disability that usually is quite prolonged, and preventing the development of permanent deformities. When these cases are treated by fever therapy at the onset of the disease, the majority are cured before any deformity results.

Atrophic Arthritis. Since chronic infectious, atrophic, rheumatoid arthritis has been so resistant to treatment, it is natural that we should see more cases of this type in our fever therapy department than of other types of arthritis. Due to the fact that these individuals have tried so many types of therapy without benefit, and because of the extreme discomfort and disability they suffer, they naturally are anxious to try any new type of treatment that may be of benefit. After reading the reports of various observers concerning results in the treatment of this type of arthritis and the small percentage of patients that were benefited,[4] we concluded that fever therapy in itself would not be of great benefit to this group. We believe atrophic arthritis is a disease of the entire body, of which the joint manifestations are only a part, and that in order to benefit these cases the general condition of the patient is of more importance than any type of treatment directed toward the joints themselves. Most of these patients show evidence of active infection, such as leukocytosis, mild fever and increased sedimentation rate; many show a marked secondary anemia, loss of weight and muscular atrophy—evidence of vasomotor instability and various nervous manifestations. Therefore we have used fever therapy in this group largely as an adjuvant to other types of treatment.

To date we have treated 82 cases of atrophic arthritis with fever therapy in combination with other forms of therapy. Of this group there were only 36 cases with definite diagnostic criteria, plus adequate follow-up data for a period of 6 months or longer; 11 were males and 25 females. Their ages range from 15 to 66 (average 40.7). The duration of the disease was from 4 months to 18 years (average 5.7). There were all types of involvement, the severity of which ranged from simple monoarticular involvement to complete disability. The average number of hours of fever above 103° was 22.4. The results obtained were graded according to clinical results, based on relief of pain, relief of stiffness and relief of swelling and deformity of affected joints. In this group we found our results as follows:

	None.	Slight.	Moderate.	Marked.
Relief of pain	22	11.0	25.0	42
Relief of stiffness	22	0	25.0	53
Relief of swelling and deformity	33	19.4	16.6	31

We furthermore tabulated our results under the heading of improvement of general condition, including laboratory as well as clinical data to support this conclusion. The laboratory data included an elevation in the red blood cell count after treatment in those that had showed a moderate or marked anemia, a decrease in

the blood sedimentation rate, the disappearance of febrile reactions and a decrease in the white blood cell count. The clinical good results were evaluated according to the general wellbeing on the part of the patient, a decrease in the amount of disability, and an increase in weight in those who were underweight. We were able to show in these cases an improvement in 78% of all the patients treated.

Practically all of the cases which were treated had formerly availed themselves of all the ordinarily accepted types of therapy, such as rest, internal medication, vaccines, visits to hot springs, massage, diathermy, and various other types of therapy. In all the cases seen in our department, after careful examination and Roentgen ray studies, 81% of these cases had already had all demonstrable foci of infection eradicated.

The adjuvant treatment consisted of iron or liver therapy or both, for those with anemia, some form of salicylates to relieve pain, high vitamin and high caloric diets for those patients who were underweight, limited diets with an attempt to reduce weight in those that were overweight, the administration of various vitamins in the form of cod liver oil, viosterol, yeast tablets or concentrates of A, B, and D vitamins. A small group of patients were put on large doses of vitamin D, *i. e.*, up to 200,000 units a day, and the fever treatments were given in groups. Four to 6 treatments at 103 to 104.5° F. were given at 5 to 7-day intervals. Following a rest period of 6 to 10 weeks, patients were given another group of fever therapy treatments if unimproved.

Of the cases that were treated by fever therapy the percentage of those with severe deformities was very high, and we soon learned that one of the most important treatments in this type of disease was the correction by orthopedic measures of existing deformities; and the prevention of deformities in those cases that had none. We feel that this phase is one of the most important in the treatment of this type of arthritis. We also found that daily massage of the atrophied muscles was very essential and very helpful. The best results were obtained in those cases which presented themselves in the poorest physical condition; that is, cases with marked anemia and extreme underweight showed very marked improvement from treatment of anemia and increasing the weight by dietary measures and the use of insulin. By improving the general condition of the patients, we also improved their ability to tolerate the discomforts of this disease.

Conclusion. We feel that artificial fever therapy is of considerable value as an adjuvant in the treatment of chronic atrophic arthritis; that it decreases general disability and swelling of the affected joints in a large percentage of cases; but that it is only an adjuvant and that the prime consideration in all cases is the additional treatment of the patients' general condition, together with proper orthopedic supervision and correction when necessary. In order ultimately

to evaluate the rôle of fever therapy, a larger number of patients must be studied over a much longer period of time than has been possible thus far.

Hypertrophic Arthritis. If we accept that hypertrophic arthritis is a degenerative rather than an infectious disease due to advancing age and strain on affected joints from overweight, occupation, trauma and like factors, it is not surprising that our results with artificial fever therapy are the most unfavorable of any of the arthritides. At present, 10 cases treated in our fever therapy department have sufficient diagnostic and follow-up data to report—6 males and 4 females, the ages ranging from 38 to 75 years, and the duration of the disease from 1 to 30 years.

The results reported in the literature by other groups were so devoid of promise[2-4] that all these patients were treated only after being advised of the very doubtful prospects of any permanent benefit. These cases were given treatments of fever of 103 to 105° F., the length of the treatment being 3 to 4 hours. Of this group 5 cases (50%) were not benefited; 1 (10%) was markedly improved; 2 (20%) were moderately improved; and 2 (20%) were slightly improved. These figures represent the results some months after stopping fever therapy. Practically all cases were improved directly after the treatments, but this improvement was only transitory and the pains returned in a few days or a week.

Conclusion. We think that fever therapy is of very little value in the usual uncomplicated case of hypertrophic arthritis. We believe, however, that those cases of hypertrophic arthritis aggravated by superimposed trauma or infection are quite often benefited by fever therapy.

Summary. 1. Of 9 cases of acute rheumatic fever with active endocarditis, 6 became inactive in an average of 24 days, following an average of 5 fever treatments. Three cases of acute rheumatic fever with active endocarditis and complicated by chorea became inactive in an average of 46 days, following an average of 9 fever treatments. We think this is a marked improvement over any other type of therapy now used and justifies further investigation of this method of treatment.

2. Of 23 cases of gonorrheal arthritis, 82% were cured or markedly improved after an average of 26.4 hours of fever maintained between 106 and 107° F. We believe that a minimum of at least 25 hours of fever of this elevation is necessary before concluding this therapy is a failure. It is the best type of therapy known to date, and should be instituted early. Orthopedic measures may be necessary.

3. We believe artificial fever therapy is a valuable adjuvant, along with dietary, supportive, and orthopedic measures, in the treatment of atrophic arthritis. This combination of treatment was of benefit in 78% of patients treated.

4. Hypertrophic arthritis is benefited by artificial fever therapy only in those cases where there is a superimposed traumatic and infectious element.

5. In any type of arthritis, with or without an infectious element, we think that heat, the oldest known and most universally applied type of therapy, is a justifiable therapeutic measure. Other means of producing febrile reactions are not so efficiently controlled nor so safe, in our opinion, as mechanically induced fever therapy. The beneficial effects of fever therapy in the arthritides, with the possible exception of gonorrheal arthritis, are in all probability not solely bactericidal, but rather the result of the beneficial effects of vasodilatation and increased immunologic response.

6. Artificial fever therapy should be given only by physicians and nurses who have received adequate preliminary training. Such treatment is not adaptable to office practice.

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STUDIES IN SYPHILITIC CARDIOVASCULAR DISEASE.

I. Uncomplicated Syphilitic Aortitis: An Asymptomatic Condition.

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There are few conditions in which early diagnosis is of greater importance than in syphilitic involvement of the cardiovascular system. The accomplishments of recent years that have been made in the specific treatment of syphilis, and especially in the technique of the therapeutic management of its cardiovascular complications, have rendered prompt institution of proper treatment of even greater moment than heretofore. The predilection of syphilis for the cardiovascular system, its distribution through vascular channels, and the premature and tragic consequences of syphilitic cardiovascular disease have long been known. Only recently, however, have adequate therapeutic methods been available, sufficiently effective in their results to outweigh the dangers inherent in their use. Because

so much depends upon the stage of the disease in which treatment is begun, it is therefore of paramount importance that the diagnosis be established before any complications have arisen; that is, while the pathologic process is still one of an uncomplicated syphilitic aortitis.

The recognition of syphilitic aortitis as a progressive pathologic process is necessary before its uncomplicated stage can be defined. Simple invasion of the aorta by the *Treponema pallidum* is possibly universal in all untreated syphilitics. Actual demonstrable involvement, gross or microscopic, has been found in a large percentage of syphilitic subjects coming to necropsy, Warthin[6] reporting 90% in 490 postmortem examinations, and Langer[3] maintaining that from 70% to 80% of adult syphilitics show evidence of such involvement. From the stage of barely demonstrable involvement, gradual progression may take place until the aortic valves are so distorted as to produce regurgitation; or the syphilitic aortitis may result in weakening of the wall of the aorta with dilatation and aneurysm formation; or the proliferative process may so encroach upon the ostia of the coronary vessels that the circulation to the heart muscle is impaired. If, however, none of these three possibilities has occurred, and if the pathologic process is limited in its distribution to the aortic wall, the condition may then be regarded as an uncomplicated syphilitic aortitis.

Recently, the various symptoms and physical signs ascribed to syphilitic aortitis have been reviewed by Moore, Danglade and Reisinger[5] in a study of the clinical records of patients in whom the diagnosis was established at autopsy. They have tabulated, in order of relative importance, the following criteria for the diagnosis of uncomplicated syphilitic aortitis: 1, Teleroentgenographic and fluoroscopic evidence of aortic dilatation; 2, a tympanitic, bell-like, tambour accentuation of the aortic second sound; 3, a history of circulatory embarrassment; 4, increased retromanubrial dullness; 5, progressive cardiac failure; 6, substernal pain; 7, paroxysmal dyspnea. They further suggest that the presence of 3 or more of these symptoms and signs in a young adult syphilitic patient without mitral disease or hypertension is strong evidence for the diagnosis of uncomplicated syphilitic aortitis. These diagnostic criteria have been adopted by the Coöperative Clinical Group now engaged in the study of the treatment of syphilis, and are reported by Cole and Usilton[1] as those on which the diagnosis of uncomplicated syphilitic aortitis has been made in their patients.

The physical signs enumerated above are incontestably those of syphilitic disease of the aorta and are all dependent upon aortic dilatation. On the other hand, the so-called characteristic symptoms of syphilitic aortitis are by no means indisputable and the validity of ascribing certain of these symptoms to a purely uncomplicated aortitis has been seriously questioned. Keefer and Resnik,[2] in a

review of the clinical and necropsy records from the medical clinic of the Johns Hopkins Hospital, found that in 24 cases of uncomplicated syphilitic aortitis, not one had shown dyspnea on exertion, paroxysmal dyspnea or signs of myocardial insufficiency. Every case of aortitis in which one or more of these symptoms were found had some additional factor to which the symptom was due—aortic insufficiency, aneurysm, myocarditis, hypertensive cardiovascular disease, or an organic obstructive lesion. More recently, in a study of 346 cases from the Brooklyn Hospital, Maynard and his associates[4] conclude that myocardial failure appears only after the development of complications and that it is not due to an uncomplicated aortitis. While these symptoms—the story of circulatory embarrassment, progressive heart failure, substernal pain, and paroxysmal dyspnea—have long been regarded as typical of syphilitic disease of the aorta and are to be found in the usual description of the condition, adequate explanation for them has not been advanced and reasonable physiologic mechanisms on which they might depend have not been suggested. A study of the symptoms of uncomplicated syphilitic aortitis therefore seems warranted in order to ascertain whether they depend on the aortic disease *per se* or upon other factors.

Material and Methods. During the past 9½ years, postmortem examinations have been carried out on 1619 patients from the Roper Hospital. This period has been chosen for study merely for the reason that adequate pathologic records are not available for autopsies performed previous to 1927. Of this number, gross or microscopic evidence of syphilitic involvement of the aorta has been found in 211 cases (13%). The clinical and pathologic records of these patients form the basis of the present study. Three complications of syphilitic aortitis have been recognized: 1, deformity of the aortic valves with regurgitation; 2, thoracic aneurysm; 3, narrowing of the ostia of one or both of the coronary arteries by the specific process. The remaining cases have all been considered as uncomplicated syphilitic aortitis. The incidence of the various symptoms in these different groups is shown in Table 1.

TABLE 1.—INCIDENCE OF SYMPTOMS IN SYPHILITIC AORTITIS.

	Total cases.*	Dyspnea on exertion.	Paroxysmal dyspnea.	Precordial pain.	Congestive heart failure.
With aortic insufficiency	49	49	14	10	49
With thoracic aneurysm	31	24	5	7	13
With narrowing of coronary ostia	21	20	5	8	15
Uncomplicated syphilitic aortitis	106	44	4	5	34
Inadequate history	17				

* Thirteen patients had more than one of the complications of syphilitic aortitis, *i. e.*, aortic insufficiency, aneurysm, or coronary involvement.

In evaluating the symptoms of uncomplicated syphilitic aortitis, it is first necessary to distinguish between those cases in which the condition occurs alone and those in which it is associated with other

cardiovascular disease or with lesions which might give rise to a similar symptomatology. Myocardial insufficiency or congestive heart failure from any cause is characterized by dyspnea and evidence of circulatory embarrassment; in those conditions in which the greater strain has been thrown on the left ventricle, paroxysmal dyspnea is not infrequently present. Similarly, tracheal or bronchial obstruction by any intrathoracic tumor, or interference by pressure with the return flow of blood to the right atrium of the heart, will cause like symptoms. Because of this, it is essential further to subdivide the group of cases of uncomplicated syphilitic aortitis to show whether or not other such associated conditions were present. Symptom analysis of the cases in these groups are summarized in Table 2.

TABLE 2.—ANALYSIS OF SYMPTOMS IN CONDITIONS ASSOCIATED WITH UNCOMPLICATED SYPHILITIC AORTITIS.

	Total cases.	Dyspnea on exertion.	Paroxysmal dyspnea.	Precordial pain.	Congestive heart failure.
Hypertensive heart disease	29	29	2	4	28
Chronic nephritis	7	5	1	0	3
Coronary heart disease	5	5	1	1	1
Chronic myocardial degeneration	2	1	0	0	0
Tuberculous pericarditis	1	1	0	0	1
Obstructive lesions	2	2	0	0	1
Without other cardiovascular disease	60	1	0	0	0
Totals	106	44	4	5	34

Comment. Table 2 requires but little comment. The 2 cases classed as chronic myocardial degeneration were probably the end-result of hypertensive cardiovascular disease, although none of the blood-pressure readings obtained during life were elevated. In all of the hypertensive cases both clinical observation and pathologic findings were indicative of the diagnosis. The 7 cases of chronic nephritis were all hypertensive and showed secondary cardiac involvement. The 2 cases with obstructive lesions, one a carcinoma of the larynx and the other a gumma of the neck, both died as a result of respiratory embarrassment. In the group with coronary artery disease 1 case of thrombosis is included, the others merely having had arteriosclerotic changes in the vessel walls, with secondary myocardial damage.

The symptoms under discussion are readily seen to occur, but wherever they are present another reasonable cause for their occurrence is at hand. These are all symptoms of circulatory insufficency, and where definite myocardial disease is present, it is more logical to believe that the latter is responsible, rather than the mere presence of pathologic changes in the aorta. Only 1 case of simple syphilitic aortitis was observed in which any of these symptoms were present where it could not be explained on the basis of

other cardiovascular disease or an organic obstructive lesion. The lone exception was a case of acute leukemia, and it seems reasonable to assume that the dyspnea on exertion from which this patient suffered was due to his anemia. In every other instance in which any of these symptoms were observed, coexisting disease was found at autopsy which offered an explanation more logical than the mere presence of syphilitic aortitis.

The following case abstracts illustrate the type of case encountered in this series:

CASE 1.—A 55-year-old negro man gave a story of gradually increasing weakness, headache, and dizziness for 1 year prior to his admission to the hospital. Three days before entry, he had a generalized convulsion. There had been no symptoms referable to the cardiovascular system. Examination showed some arteriosclerosis; blood pressure 120/70; heart normal in size, with some supracardiac widening. The blood Wassermann reaction was positive, the spinal fluid examination negative. Convulsions returned, fever appeared, the lungs filled, and the patient died 1 week after entry. Autopsy showed a chronic encephalitis, possibly syphilitic in origin, and bronchopneumonia. The heart was not enlarged. The aorta was widely dilated, its walls thin and inelastic, with scarring typical of syphilitic aortitis.

CASE 2.—A 28-year-old negro man had had a right inguinal hernia for about 1 year when it became incarcerated and irreducible. He had no other symptoms. Physical examination was not remarkable except for moderate widening of the area of retromanubrial dullness. After operation the patient developed a constant fever, 100 to 103° daily. Roentgen ray of the chest showed a widened aorta and some indefinite clouding at the base of the left lung. Three weeks after operation the patient died. Autopsy revealed tuberculosis of the retroperitoneal lymph glands, and miliary tuberculosis of the lungs, liver and spleen. The heart was normal on both gross and histologic examination. The aorta was dilated and considerably scarred, microscopically showing lesions typical of syphilitic involvement.

CASE 3.—A 55-year-old negro man gave a history of illness for 1 month with chills, fever, sweats, and severe headache. There were no cardiac symptoms. Physical examination was negative except for generalized glandular enlargement and a positive Romberg sign. The spinal fluid contained 164 cells, largely lymphocytes, a normal amount of sugar, and gave a positive Wassermann reaction with 1 cc. The patient's symptoms were relieved by lumbar puncture, and repeated spinal taps showed an essentially similar fluid. Terminal bronchopneumonia was the immediate cause of death 2 weeks after entry. Pathologic diagnosis at autopsy included: chronic pulmonary tuberculosis; acute lobular pneumonia; acute miliary tuberculosis of the liver, spleen, kidneys and lymph glands; tuberculous meningitis. The aorta was dilated and scarred, with microscopic lesions typical of syphilitic involvement.

In the 2 cases presented below, cardiovascular disease other than syphilitic aortitis was found at autopsy which would account for the patient's symptoms:

CASE 4.—A 30-year-old negro man entered the hospital with a story of intermittent attacks of pain in the left abdomen and back for 2 months, with the subsequent appearance of hematuria, dysuria, polyuria, loss of weight, and hiccough. There had been some dyspnea on exertion for 2 months, and vague chest pain for 2 weeks. Examination showed nothing of note except a blood pressure of 87/64. Roentgen ray of the chest was normal. The blood urea nitrogen was 181. Because the urine was thought

to be contaminated with feces and because intestinal obstruction was suspected, abdominal exploration was decided upon, and the patient died on the operating table. At autopsy, pyelonephritis and bronchopneumonia were found. There was marked fibrosis of the heart, without enlargement. The wall of the aorta was thick, rough and scarred and microscopic study corroborated the diagnosis of syphilitic aortitis.

CASE 5.—A 49-year-old negro woman gave a story of swelling of the ankles and dyspnea on exertion of 1 year's duration, cough, palpitation, and precordial pain. On examination the heart showed no abnormalities. Blood pressure was 108/62. There was some fluid accumulation at the base of both pleural cavities, which was shown by Roentgen ray, the latter revealing also some cardiac enlargement and aortic widening. The edema disappeared on rest but later returned, and the patient eventually died of heart failure. A guinea pig, inoculated with chest fluid, developed no tuberculous lesions. Autopsy showed tuberculous pericarditis, with considerable enlargement of the heart and complete obliteration of the pericardial cavity. The aorta was scarred with lesions typical of syphilitic aortitis and was moderately dilated.

Analysis of a group of these cases from a slightly different point of view gives a significant result. There were 11 known syphilitic patients who suffered from 1 or more of the symptoms under discussion, who had no evidence of hypertension, mitral disease, or either of the clinically demonstrable complications of syphilitic aortitis—thoracic aneurysm or aortic insufficiency. All of these patients had dyspnea on exertion, 1 had paroxysmal dyspnea, 3 gave a definite history of precordial pain, and 3 were seen with congestive heart failure. Widening of the area of supracardiac dullness was noted in 7 cases, and in each of the 3 patients examined by Roentgen ray, aortic dilatation was found. On the basis of the previously mentioned diagnostic criteria,[5] the symptoms of all of these cases might have suggested the diagnosis of syphilitic aortitis, particularly in those in which evidence of aortic dilatation was found. However, in addition to the syphilitic aortitis, in every instance coronary artery disease was demonstrated at autopsy, 6 patients showing syphilitic involvement with partial or complete occlusion of one or both of the coronary ostia, and the remaining 5 cases showing coronary sclerosis. Here again, it is more reasonable to ascribe the symptoms to the coronary disease with its attending myocardial involvement, than to aortic disease.

Brief summaries of 2 of these cases are presented herewith:

CASE 6.—A 24-year-old negro man entered the hospital with a story of severe and rapidly increasing dyspnea of 1 month's duration, edema for 3 weeks, sleeplessness, and aching precordial pain. The blood pressure was 130/60. The heart was slightly enlarged, with an apical systolic murmur. Râles at the bases of the lungs, an enlarged liver, and general edema were other positive physical findings. A Roentgen ray showed generalized enlargement of the heart and aorta. Electrocardiogram interpretation revealed right axis deviation. The patient did not improve and died 2 weeks after entry. Autopsy showed considerable enlargement of the heart, especially of the left ventricle, and dilatation of the right. There was no demonstrable insufficiency of the aortic valves, but the valves were thick-

ened and to the posterior cusp was attached a small thrombus. The aorta was considerably scarred by syphilitic lesions, with practically complete occlusion of the orifice of the right coronary vessel. The remainder of the artery was normal, and the left coronary artery was normal throughout.

CASE 7.—A 49-year-old negro man gave a story of chills, fever, and shortness of breath for 2 months prior to his admission to the hospital. There had been some swelling of the feet also. Signs of cavitation were noted in the right upper lobe of the lung. The heart was normal on examination, but Roentgen ray showed some enlargement with dilatation of the aorta. Autopsy showed chronic ulcerative tuberculosis of the lungs and acute bronchopneumonia. The heart was very slightly enlarged, with considerable fibrosis and some coronary sclerosis. The aorta was dilated and scarred with typical lesions of syphilitic aortitis.

It is not to be argued that in many of the 60 asymptomatic cases of uncomplicated syphilitic aortitis could the clinical diagnosis have been made. The degree of involvement of the aorta found at autopsy in this group showed considerable variation. Marked dilatation was found in only 3 cases, moderate dilatation in 7, slight in 10, and a normal-sized aorta was noted in 40 instances. Extensive pathologic involvement was seen in 12, moderate in 27, and only slight involvement in the remaining 21 cases. One would hardly expect symptoms to have occurred in cases in which there was only minimal involvement of the aorta. But this is precisely the stage in which specific treatment should be able to accomplish the most, and so prevent further extension of the process as to render the development of complications unlikely. And if the available methods of symptom analysis and physical examination are inadequate to allow a diagnosis to be made definitely in this stage, their usefulness is necessarily limited. In this group of cases* the diagnosis of syphilitic aortitis was not made in a single instance, and on reviewing the pathologic findings it is difficult to pick out more than a few cases in which it would seem possible to have done so. And yet this is the group in which early diagnosis is of such importance if the most is to be obtained by antisyphilitic therapy.

On the basis of this analysis, it seems reasonable to assume that uncomplicated syphilitic aortitis is an asymptomatic condition. When cardiac or respiratory symptoms occur, they have been shown in every instance to be due to some factor other than the simple aortic disease, that is to say, either to an extension or complication of the syphilitic process or to some entirely unrelated condition. If we accept this conclusion, it becomes quite clear just why so much difficulty is experienced in making the diagnosis of uncomplicated syphilitic aortitis. There are no symptoms referable to the cardio-

* The cause of death in these patients was lobar pneumonia in 11, cerebral hemorrhage in 10, abdominal aneurysm in 5, carcinoma (various) in 5, pulmonary tuberculosis in 4, various acute surgical abdominal conditions in 4, C. N. S. syphilis in 3; 2 each died of pyelonephritis, urinary extravasation, fractured skull, septicemia, pellagra, and peptic ulcer with hemorrhage; 1 died of each of the following: acute nephritis, CCl_4 poisoning, encephalitis, tuberculous meningitis, acute leukemia and acute yellow atrophy.

vascular system, the patient does not as a rule seek medical attention, and the physical signs are such that they might be easily missed on casual examination. The importance of thorough clinical and roentgenologic study cannot be overemphasized, for by these methods alone can the diagnosis be established before the condition has progressed so far as to prevent the best results being obtained by specific treatment. Accurate diagnosis depends, therefore, upon the realization that cardiac or respiratory symptoms are significant of either a complication of the original condition or of some other coexisting disease; only when every adult syphilitic patient is regarded as a possible victim of syphilitic aortitis and only when every available method is used for the detection of beginning aortic dilatation will the diagnosis of truly uncomplicated syphilitic aortitis become clinically possible.

Summary. Two hundred and eleven cases of syphilitic aortitis, proven at autopsy, have been analyzed with regard to presenting symptoms. In practically every case in which cardiac or respiratory symptoms were present, they have been shown to be due to some factor other than uncomplicated syphilitic aortitis—either to an extension or complication of the syphilitic process or to some coexisting disease. It is concluded that uncomplicated syphilitic aortitis is an asymptomatic condition, and that no criteria dependent upon symptoms are reliable in making an early diagnosis.

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IDIOPATHIC MYOCARDIAL DEGENERATION ASSOCIATED WITH PREGNANCY AND ESPECIALLY THE PUERPERIUM.

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The effect of pregnancy on the heart has been a subject of considerable interest and has been discussed from many viewpoints. There is, however, one feature of cardiac disease of pregnancy

which has never received consistent attention: namely, the existence of an idiopathic myocardial lesion associated with the puerperium. That degeneration of the myocardium may be caused by pregnancy and the puerperium was surmised many years ago, but this association has never received general recognition. Among earlier writers, both Virchow[10] and Porak[6] pointed out that myocardial degeneration was not an uncommon finding in women who died in the puerperium, the former stating that the change might reach a degree comparable to that seen in classical phosphorus poisoning. More recently, Blacker[2] (1907) and Campbell[3] (1923) have pointed out that myocardial disease unaccompanied by valvular lesions was important in producing cardiac failure during and after pregnancy. Williams[12] (1933) stated that 1.5% of cardiac deaths during and soon after pregnancy are the result of an "idiopathic myocarditis." Hermann and King[5] (1930), in discussing the various forms of heart disease associated with pregnancy, described 4 patients who developed severe myocardial disease during the puerperium which proved fatal in 3 instances. We regard their observations as important, for during the last 4 years we have observed in 7 patients severe puerperal heart failure of a strikingly similar type. The clinical and pathologic findings in 4 of these patients are the basis of this report of what, in our opinion, is an unusual myocardial lesion.

In all of our patients, heart failure, developing insidiously in the late months of pregnancy, assumed serious and stubborn proportions during the puerperium. The clinical features were dyspnea, edema, cardiac enlargement, cyanosis, and gallop rhythm. Murmurs were not conspicuous and precordial pain was absent. Embolism was a common development, being the immediate precipitating cause of death in 3 patients and occurring probably in all of our recovered cases.

Necropsy consistently revealed gross evidence of severe myocardial disease of recent origin. Histologic study confirmed this and showed it to consist of widespread and severe focal inflammatory reaction often with necrosis and followed by fibrosis.

Another striking feature was the development of mural thrombi in the heart, secondary either to foci of subendocardial myocarditis or to myocardial dilatation and subsequent thrombus formation in the mural columnar meshwork. This was the obvious source of embolism, which was so frequent a development.

Case Reports. CASE 1.—J. C., Italian, aged 23, whose past medical history was irrelevant, suffered from dyspnea, cough, fatigue, and edema in the 8th month of her first pregnancy. These evidences of heart failure apparently disappeared after delivery on September 12, 1930, only to reappear in greater intensity upon the resumption of her usual household duties. The heart failure gradually progressed and eventually necessitated her admission to the Philadelphia General Hospital, service of Dr. David Riesman, on January 3, 1931.

Examination revealed pulmonary congestion, an enlarged liver, and peripheral edema. The heart was moderately enlarged, its rate rapid, its rhythm regular. No murmurs were detected, but a gallop rhythm was present over the apical area. The blood pressure was 105 systolic, 70 diastolic. The blood count showed 3,300,000 erythrocytes, 75% hemoglobin, 12,000 leukocytes. The blood culture and urinalysis were negative, and the blood chemical studies and serum protein determination were all within normal limits. The electrocardiogram showed low amplitude, shaded ventricular complexes in all leads, with inverted *T* waves in Leads 2 and 3.

During the first week of our observation, the patient's condition improved slightly. The temperature, never high, soon returned to normal, and the pulse rate varied between 80 and 110. The patient's weakness, however, did not appreciably lessen, and the gallop rhythm persisted. A search for focal infection, dental and gynecologic, was unsuccessful. On January 28, the patient developed a burning pain in the left upper abdomen. This soon disappeared, but a similar attack occurred the following day, after which the spleen became palpable and tender. On February 5, there developed an attack of severe, sudden, upper abdominal pain, during which the leukocyte count rose to 35,000, persistalsis became absent, the abdominal wall rigid, and distention marked. Death occurred on the following day, February 6, and was attributed to mesenteric thrombosis.

Necropsy (Dr. Gunn, 5 hours after death). The heart, weighing 500 gm., was globular in shape and enlarged in its transverse diameter. The epicardium was smooth and glistening. Both ventricles were dilated and the left ventribular wall was moderately hypertrophied. The muscle was pale, grayish-brown, soft, and mottled by congestion. Near the apex, on the septal wall, adherent in the meshwork of the columnæ carneæ, was a reddish-brown thrombus, about the size of a nickel; the underlying muscle was soft and clouded. The right ventricle presented the same muscle changes noted in the left chamber, but no thrombi were present. There were no valvular lesions aside from relative insufficiency of the mitral ring. The fossa ovalis was closed.

The aorta was of normal appearance throughout. The coronary arteries were patulous, their intimal surface entirely smooth.

All the viscera showed an acute passive congestion, in addition to which there were hemorrhagic infarctions of the spleen and kidneys and mesenteric thrombosis which, with subsequent peritonitis, was the immediate cause of death.

Histology. Sections from the septum, the midportion of the posterior wall of the left ventricle and anterior papillary muscle all exhibit the same pathologic changes. The myocardium shows in many areas a marked parenchymatous degeneration; the muscle fibers are irregularly sacculated, and wavy because of the loss of cytoplasmic content. In some fields, muscle fibers and their nuclei appear slightly thicker than normal, suggesting a previous state of hypertrophy.

Necrotic foci, both large and small, are noted in a number of fields. The lesion shows more or less cellular infiltration by lymphocytes, occasional eosinophils and neutrophils, and larger cells with irregularly oblong and cuboid nuclei (Figs. 1 and 2). These are apparently nuclei of heart muscle, some being surrounded by sarcoplasm in a decadent state; at the periphery of such a focal lesion and in the adjacent myocardium, an earlier stage of the myocardial destruction is noted in which the myocardial cytoplasm can be seen to be disappearing, leaving behind the isolated nuclei (Fig. 2). Occasionally two or three myogenic nuclei are closely clumped together, probably representing an effort at myocardial regeneration. Some of the arterioles and venules show a slight hyperplasia of the lining endothelium; aside from this, there is no vascular damage.

The endocardium in some places is swollen by edema. These swellings contain a considerable amount of fibrinous deposit and some round and endothelial cell infiltration. The overlying endothelial layer shows disruption in a few areas with deposition of small amounts of fibrin.

CASE 2.—J. M., Polish, aged 38, had had 6 pregnancies during 11 years, during each of which she went through an episode which was diagnosed as nephritis. During the 5th pregnancy, breathlessness and edema were apparently marked, and the blood pressure was found to be high. Her 6th and last pregnancy terminated on November 21, 1931, with no complications except rather severe postpartum hemorrhage. Instead of the usual puerperal recovery, breathlessness, weakness and edema appeared and became progressively worse, and ultimately led to her admission to the Philadelphia General Hospital, service of Dr. A. A. Stevens, on January 15, 1932.

Congestive heart failure was evidenced by orthopnea, cyanosis, greatly distended neck veins, pulmonary and hepatic congestion, ascites, and marked leg edema. The heart was overactive and definitely enlarged, both by percussion and Roentgen ray examination (Dr. H. Ostrum). No murmurs were heard, but a prominent gallop was demonstrable over the apical area. The cardiac rhythm was regular. The blood pressure was 162 systolic and 124 diastolic.

Pelvic examination revealed nothing abnormal. The blood count, the Wassermann test, and the urinalysis were normal. The blood sugar was 100 mg.%, and the blood urea nitrogen 11 mg.%.

During the first few days of hospitalization, there was considerable improvement, but the gallop rhythm persisted. On January 31, 1932, the temperature rather suddenly rose to 102° F., the pulse to 140, and the respirations to 33 per minute. Signs of consolidation in both lower lobes, accompanied by a right-sided friction rub, suggested the early development of pneumonia, though the possibility of infarction was considered. The temperature soon declined and on February 8 was normal; but the pulse rate remained high and the leg edema, which had never subsided, progressively increased, and the right arm began to swell.

Death occurred on February 19, 1932. The cardiac failure was well recognized, but the character of the pulmonary consolidations remained doubtful, and the final clinical diagnosis was recorded as lobar pneumonia and myocardial degeneration following pregnancy with extreme cardiac decompensation.

Necropsy (Dr. William Brody, 13 hours after death). The significant changes involved mainly the cardiovascular system.

The heart was considerably enlarged, weighing 480 gm. The left ventricle was both hypertrophied and dilated, its wall in its midportion measuring 18 mm. The muscle was very soft and pale. The right ventricle, similarly dilated but not hypertrophied, showed the same pallor and softness. At the apex of this chamber were soft, white, loosely attached antemortem thrombi. No definite auricular thrombus formation was noted. The foramen ovale was completely closed. The coronary vessels were smooth and patulous throughout, and the aorta showed nothing of importance.

There was marked passive congestion of the viscera, in addition to which there were bilateral hydrothorax, large multiple hemorrhagic infarctions of both lungs, infarction of the liver, acute multiple ulcerations in the lower ileum and ileocecal junction, which on microscopic examination proved to be due to thrombotic occlusions of sclerotic mesenteric arterial branches.

A small, old, and firmly attached aseptic thrombus was found in one of the ovarian veins, apparently of the type seen so often after pregnancy in the tortuous veins of the broad ligaments. We regarded it as inactive and not in any way the cause of the cardiac decompensation, the massive pulmonary infarctions, or the systemic embolism.

The kidneys showed a mild nephrosclerosis and passive congestion.

Histology. The epicardium is normal. Sections from both the left and right ventricle show marked parenchymatous degeneration associated with considerable interstitial edema. In many areas, the myocardial fibers have become thin and of irregular width due to the diminution of the sarcoplasmic content; often the muscle destruction is intense so that small fragments and fibrils remain in a space devoid of any normal structure; edema and sometimes hemorrhage fill in these spaces. An occasional neutrophil is seen, but the cellular invasion is scanty; occasionally a myocardial nucleus is seen with most of the cytoplasm destroyed. In other areas, fibroblasts are invading the foci of muscular degeneration.

Some small arterial branches have definitely thickened walls, but are patulous and appear to have no relationship to the destructive change.

Kidneys. A moderate nephrosis is seen in the proximal convolutions and tubular structure. The glomeruli are congested; but there is no exudative or proliferative process suggestive of glomerulonephritis either acute or chronic. There is moderate but definite thickening of the arterioles, but no renal, parenchymal scarring is seen.

Case 3.—S. F., aged 37, the mother of 4 healthy children, began to have breathlessness, cough, and slight edema in December, 1931, in her 3d month of pregnancy. Following a 7th month miscarriage in April, 1932, the circulatory weakness increased significantly with the appearance of marked dyspnea, edema, and hemoptysis. Bed rest and medical treatment were of no avail and she was admitted to the Philadelphia General Hospital on the service of Dr. A. A. Stevens, in August, 1932. The past medical history was otherwise unimportant. Her previous pregnancies had been uneventful and there was no history of rheumatic or other infection.

On admission, the patient showed extreme congestive heart failure, which necessitated thoracentesis, paracentesis abdominalis, venesection, and the use of oxygen. These emergency measures resulted in considerable improvement. Examination on the next day showed cardiac enlargement, which was confirmed by Roentgen ray examination. There were no murmurs, but the heart sounds were rapid and embryocardial. The blood pressure was 150 systolic and 90 diastolic. An electrocardiogram revealed the presence of numerous ventricular extrasystoles, arising apparently from different foci, low amplitude of the *Q–R–S* complexes in all leads, and inverted *T* waves in Lead 1. Clinical and Roentgen ray examination of the lungs revealed at no time any change except bilateral hydrothorax.

In spite of treatment, including the use of Novasurol, some degree of anasarca was constantly present. No focal infection was found except that associated with a bed sore over the buttocks that had developed during the many months of bed confinement and which was almost certainly the source of the *Staph. aureus* bacteremia that appeared a few days before death on September 17, 1932. The Wassermann reaction, the blood-sugar determination, and the urinalyses were normal. The blood urea nitrogen ranged between 9 and 16 mg.%; blood creatinine was 1.8 mg.%. The blood count revealed 3,750,000 erythrocytes and 17,400 leukocytes with a 90% neutrophil count. The clinical diagnosis was chronic myocarditis, possibly of the Fiedler type, with severe circulatory failure, decubitus, and septicemia.

Necropsy (Dr. Kennedy, 12 hours after death). The heart weighed 510 gm., was considerably enlarged, of globular shape, and exceedingly soft. The dilatation far overshadowed whatever previous hypertrophy had existed. On repeated section, the myocardium showed a marked parenchymatous degeneration, being pale, brownish-gray, and in the papillary muscles, a dirty putty color. Fine scarring was noted throughout. The right ventricle was likewise soft and pale, but to a lesser degree. At its apex, however, there was a grayish-white, endocardial (mural) thrombus,

organized and continuous with a fibrotic reaction in the underlying myocardium. Both auricles were dilated, and there was a dry fleshy-red thrombus attached in the right appendage.

A small, soft, greenish flagellated thrombus (*Staph. aureus*) was rather firmly attached to the edge of the anterior mitral leaflet, which was otherwise entirely normal, showing no previous lesions.

The root of the aorta and the coronary vessels were normal. Also noted were: 1, Marked cyanotic induration of the viscera; 2, large purulent bed sores over the buttocks, and, 3, a small (30 cc.) indurated right retromammary collection of pus and milk, the possible significance of which will be discussed later.

Histology. A number of sections taken from the wall of the left ventricle anteriorly and laterally, and from the septum show the same pathologic change: a focal destruction of muscle. Some degree of hypertrophy is occasionally noted. Many of the foci are old lesions, being really acellular scars, irregular in outline, and sometimes coalescent (Fig. 4). Subacute lesions are noted in which there is cellular infiltration including large phagocytes, loaded with blood pigment. Some destruction of the myocardium goes on at the periphery of these lesions, the sarcoplasm being involved to a greater degree than the nuclei. The latter are often surrounded by small remnants of poorly striated cytoplasm or are found isolated altogether in the focal necrosis. In all sections, the large arteries are entirely normal. In some of the old scarred lesions, arterioles are found with greatly thickened walls. This, however, is not uniform and in the subacute lesion this arteriolar thickening is not present. There is no vascular occlusion, and no septic infarctions are seen. The scars have no definite relationship to the location of the vessels.

A section of the right ventricle shows an organized mural thrombus adherent to the endocardium and merging with a subchronic fibrous lesion of the myocardium, such as is described above.

Sections from the kidney show that the large majority of the glomeruli are normal. There are occasional foci of lymphocytic infiltration with scarring of the adjacent glomeruli due to arteriolar sclerosis. The small arteries and arterioles have moderately thickened walls. There are also a few small foci of suppuration apparently early abscess formations related to the bacteremia.

Case 4.—W. P., a white woman, aged 38, had mild dyspnea in the last 3 months of pregnancy, at which time a systolic mitral murmur had been noted. These were not striking, and did not interfere with the completion of pregnancy and a normal delivery on March 15, 1933. On attempting to resume her normal activities, however, 18 days after delivery, circulatory failure definitely developed and finally necessitated admission to the Philadelphia General Hospital, service of Dr. W. E. Robertson, on April 20, 1933.

Examination presented a definite but moderate degree of congestive heart failure, there being distention of the neck veins, râles at the base of the lungs, moderate breathlessness, and edema. The heart was greatly enlarged, the apical beat palpable in the fifth interspace in the anterior axillary line. The heart sounds were poorly heard at the apex, but the second pulmonic sound was greatly accentuated, and there was a systolic and presystolic apical murmur; auricular fibrillation was present. The blood-pressure reading was 110 systolic and 60 diastolic. The temperature varied from 98° to 100°, but after a few days returned to normal. The urinalysis, the Kahn test, and the blood sugar determination gave negative results. The blood urea nitrogen was 16 mg.%, and the blood count showed 3,000,000 erythrocytes, 60% hemoglobin, 10,900 leukocytes, with a differential of 76% neutrophils, and 24% lymphocytes.

The restoration of compensation was interrupted by cerebral embolism on May 24, resulting in a right-sided hemiplegia. Death occurred 6 days later. The clinical diagnosis was rheumatic heart disease, mitral stenosis, auricular fibrillation, and cerebral embolism.

Summary. A patient, aged 38, non-hypertensive, with known chronic rheumatic mitral valvulitis, developed severe congestive heart failure comparatively late in the puerperium; a slow recovery was ended by fatal cerebral embolism.

Necropsy (Dr. David Fishback, 14 hours after death). In addition to mitral stenosis, there was an unusual myocardial degeneration; namely, widespread necrosis with the formation of numerous mural thrombi in the left and right ventricles. There were multiple infarcts in the lungs, in the spleen, and thrombosis of the right cerebral artery with subsequent softening in the right motor area and internal capsule. There was widespread passive congestion, but no evidence of nephritis.

The heart was enlarged and of globular shape; the epicardial surface was entirely smooth. Section showed no hypertrophy, but the dilatation was unusual in that advanced fibro-calcareous mitral stenosis was present. The myocardium showed numerous foci of hemorrhagic necrosis throughout the lateral, the posterior, and to a lesser extent, the anterior walls. They extended into the apex. Both confluent and isolated areas of hemorrhage and softening were surrounded by less soft but putty-colored myocardium. The overlying endocardial surface was speckled with mural thrombi.

The right ventricle was moderately dilated, and its wall likewise contained isolated foci of hemorrhagic necrosis.

Both auricles were markedly dilated. No pectinate thrombi were seen. The fossa ovalis was open along its anterior edge so that a pencil could easily be passed; the fossa bulged out toward the left auricle and the free edge had a roughened appearance, being studded by fibrin; a tearing of the fossa with resultant patency was indicated. The coronary arteries, as far as gross inspection would permit, were of normal appearance.

Histology. A section of the left ventricle shows a myocardial lesion that is found in every section taken from either left or right ventricle, the septum included.

The epicardium is normal. In the myocardium are large and small foci of muscle destruction more intense and diffuse in the inner half of the myocardium but observed even in close proximity to the epicardium. Some of these areas are so large as completely to take up low-power fields. The muscle is replaced by densely cellular collections, in many places accompanied by hemorrhage. The cells, most of which are oval, usually have a striking tendency to lie in the same direction with each other and with the surrounding myocardial fibers so that one gets the impression of numerous rows almost parallel and continuous with the adjacent myocardial fibers (Fig. 5). Higher magnification shows that these rows of cells are really myogenic nuclei, left stranded by an apparently rapid loss of the sarcoplasm (Figs. 6 and 7). The compact disposition of these rows of nuclei give the impression of a state of tissue collapse. There are also present remnants of the interstitial connective tissue of the myocardium (perimysium). Comparatively few polymorphonuclears are seen; in large lesions, flooded by hemorrhage, neutrophils are present in modest numbers. In the smaller foci, a few lymphocytes are present, and young fibroblasts are seen in most of the lesions. At and near the periphery of the lesion, adjacent muscle fibers have become narrow and taper into wavy remnants which stain poorly. In this process of degeneration, the nuclei are also involved, but to a lesser degree. They are often swollen, somewhat to giant-cell dimension, in contrast to the progressive loss of the sarcoplasm and fibrils. Where there

has been hemorrhage, a number of macrophages are found filled with blood pigment.

In some areas the cellular collections have apparently disappeared, leaving an almost acellular structure consisting of a rather condensed fibrillar network containing a few connective-tissue nuclei and many congested small blood-vessels. This is apparently a subchronic stage: a collogen fibrosis secondary to the subacute stage of collapse. Where the myocardium is still preserved but obviously undergoing degeneration, the acidophilic stain gradually diminishes, fading out altogether or occasionally becoming mildly basophilic.

These focal lesions reach the endocardium, which in places is thickened by fibrosis and in other places covered by large fresh mural thrombi.

The large arteries and veins are patulous and without evidence of atheromatous degeneration (Fig. 8). In the midst of the areas of myocardial destruction, many small arteries are found to be filled with fresh blood, but not thrombosed. An occasional small vein is acutely thrombosed, but where these small vascular occlusions have developed they are recognized as very recent events, entirely out of relationship to the vast amount of destruction and the subacute character of the lesions.

In no place, despite the presence of mitral stenosis, is there a histologic change that can be ascribed to rheumatic fever.

We have observed the development of puerperal heart failure in 3 other patients, who after a stormy and prolonged puerperal convalescence, recovered with apparently complete restoration of compensation. We believe that their cardiac failure which was complicated by embolism, was identical with the condition just described. These cases, unsupported by pathologic data, have not been included, but occasional reference to them will be made in discussion of some of the clinical features of this cardiopathy.

Discussion.—We do not wish to imply that we believe the form of severe myocardial degeneration described in these cases of puerperal heart failure is specifically dependent upon pregnancy and the puerperal state. Instead, there is some evidence against such a view. We have encountered it at least twice in men.* Nevertheless, the observations of Hermann and King, and our own, make us feel that severe and often fatal myocardial degeneration which can only be called idiopathic can be directly or indirectly associated with or precipitated by pregnancy and the puerperium, and deserves emphasis.

The Course and Clinical Manifestations. These patients had symptoms suggestive of cardiac embarrassment before confinement, usually of a mild type and scarcely distinguishable from the general discomfort experienced by many women in the late months of pregnancy. In Case 3, however, the onset was early with leg edema and dyspnea appearing in the 4th month. Labor was hastened in one of the surviving patients because of rapidly developing toxemia; otherwise, the delivery in every instance (inclusive of surviving patients) was practically uneventful and certainly without those

* One such example, a man, aged 37 years, who developed heart failure following an upper respiratory infection, was recently reported by Roesler and Soloff.[7]

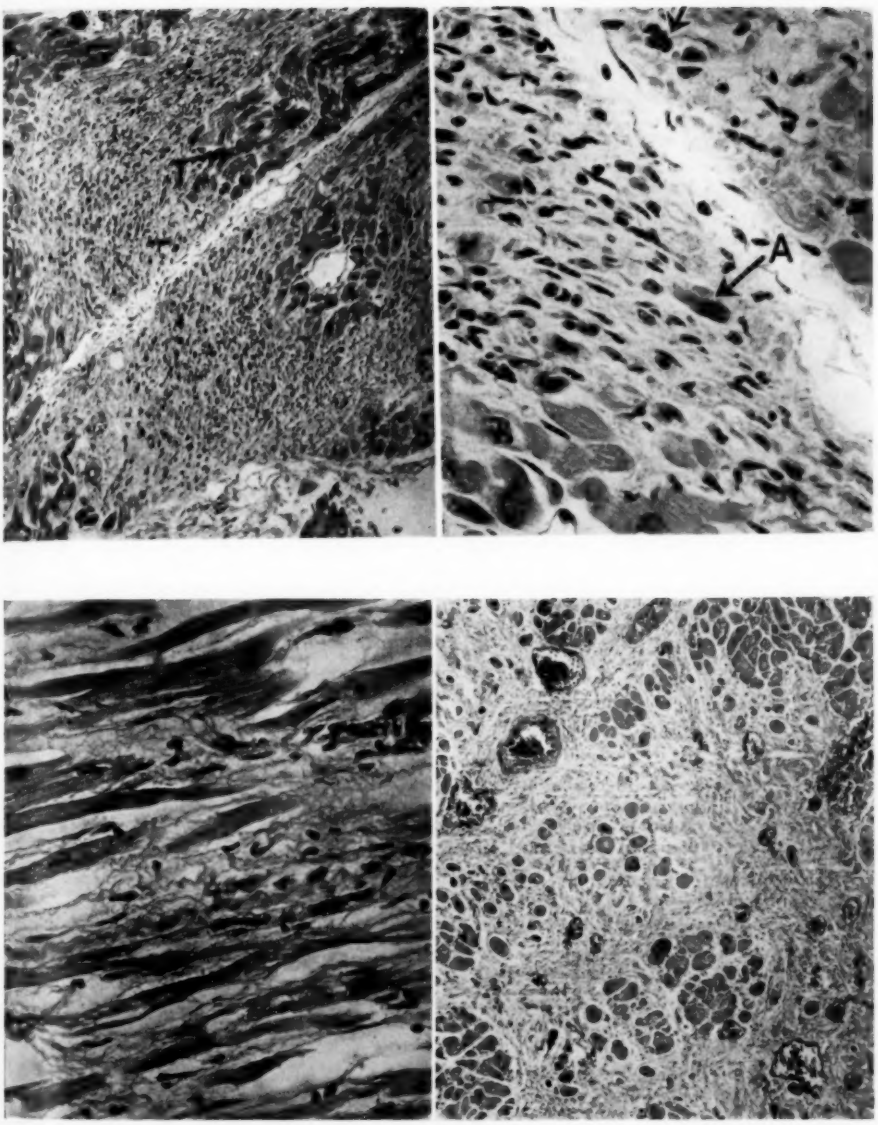
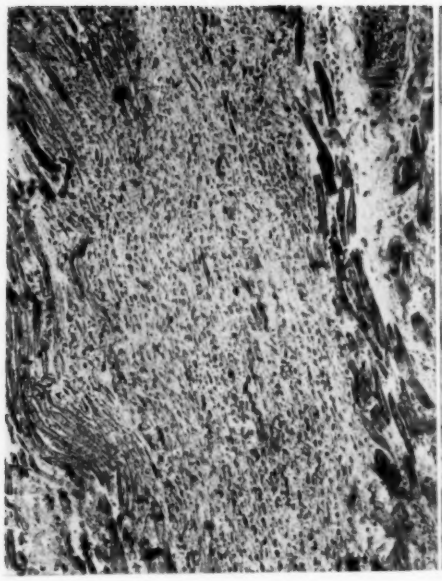


FIG. 1.—A focus of myocardial degeneration (left ventricular septum). Notice "cells" arranged in formation more or less parallel with adjacent muscle fibers. Most of these "cells" are muscle nuclei; their large size is striking even with this magnification. (×92.)

FIG. 2.—(Case 1.) Left ventricle, anterior lateral wall. Note destruction of myocardial fibers with the liberation of swollen degenerated nuclei: "A." There is a moderate number of round cells in the field, an occasional eosinophil, and also remnants of the original connective tissue. Many muscle nuclei lost in this focus and becoming progressively less characteristic, can be confused with fibroblasts. (×230.)

FIG. 3.—(Case 1.) Muscle degeneration progressing to a state of almost complete dissolution, leaving a mesh of crumpled fibrils. The degenerated nuclei are surviving the sarcoplasmic destruction. (×276.)

FIG. 4.—(Case 3.) Irregular scars, the end stage of the destructive process, in a patient who was in a state of puerperal and postpuerperal cardiac decompensation for 5 months. There are no vascular lesions. The small arteries and veins are normal. (×69.)



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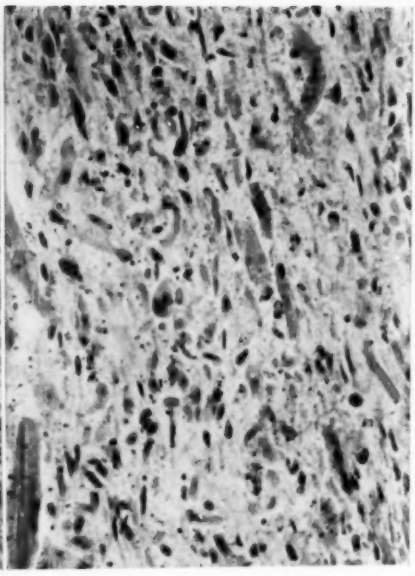

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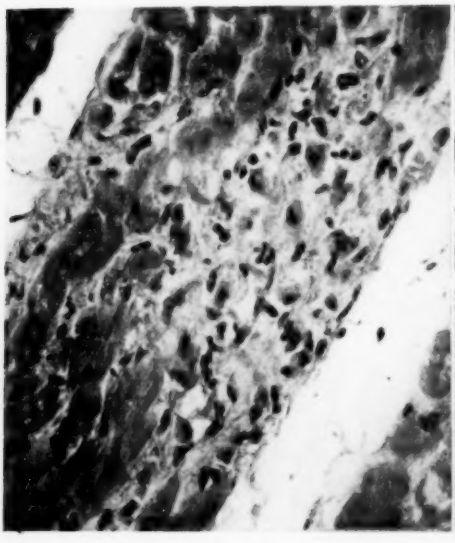

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FIG. 5.—(Case 4.) Large focus of muscle destruction occurring in the puerperium. Note tendency of the adjoining myocardium to "melt" into the destructive process, also the more or less parallel disposition of the muscle nuclei. Compare with Fig. 1 (Case 1). (×69.)

FIG. 6.—(Case 4.) Almost complete sarcolysis; a few remnants of myocardial cytoplasm remain in a "cellular focus," consisting of surviving but degenerated myogenic nuclei, perimysial tissue and a few lymphocytes. This section is unfortunately marred by a granular fixation defect. (×230.)

FIG. 7.—(Case 4.) A small focus of myocardial dissolution, "sarcolysis," entirely similar to the larger foci. (×230.)

FIG. 8.—(Case 4.) The myocardial degeneration is seen approaching the epicardium. The coronary artery is normal. (×57.)

circulatory crises—cardiac collapse, pulmonary edema—that are not uncommon in patients with mitral stenosis. Cardiac failure in all these patients developed its most serious phases during the puerperal state. In some, the puerperal rest period appeared to pass uneventfully, only to be followed by recurring heart failure after resumption of the ordinary household activities. In Case 3, and also in one of the recovered cases, heart failure was ushered in sharply soon after delivery by hemoptysis, apparently due to pulmonary infarction. Regardless of the initial development, cardiac failure was established in each case in less than 1 month following confinement.

While circulatory weakness was fairly obvious, the symptoms and signs of heart failure were complicated as in Case 1 by other symptoms suggestive of obscure inflammatory processes. Thus, in one or another case, phlebitis, pelvic infection, and subacute bacterial endocarditis were suspected.

The fever shown by these patients was usually mild, irregular, and soon subsided to a normal level, but often there was an abrupt change in the clinical course because of embolism and infarction.

Leukocyte counts varied from 10,000 to 17,000; higher counts were obtained with the development of embolism. The differential counts were not noteworthy, except in Case 3, where a high neutrophilic response was probably due to the presence of terminal bacteremia. These patients had a secondary anemia, usually moderate, However, in Case 1, the erythrocyte count was 3,000,000 and a tentative diagnosis of the so-called pernicious anemia of pregnancy was considered.

Blood cultures were done on 3 of the 4 necropsied patients. One was positive, that being a *Staph. aureus* culture that was obtained in Case 3 after the patient had been ill for several months, and which we considered to be due to a terminal bacteremia caused by an extensive bed sore.

Decompensation was unduly prolonged in our judgment in comparison with other types of heart disease with the exception of severe chronic coronary disease. Breathlessness was common to all cases, as might be expected; it was persistent and the last symptom to disappear. Edema also afforded a striking evidence of decompensation; it subsided in Case 3 before death occurred from septicemia.

Gallop rhythm, an early and conspicuous sign, was noted in 5 of 7 patients, and its early development was matched by its persistence.

The electrocardiographic studies indicated that myocardial damage had occurred in every patient, but gave no definite clue as to etiology. Inversion of the *T* waves was seen in the various leads, either singly or in combination, allowing an interpretation of "myocardial degeneration," but never positive for myocardial

infarction. The new direct chest leads were used in one of the surviving cases.

Roentgen examination invariably showed a moderate enlargement of the heart in the transverse diameter, usually associated with pulmonary congestion. No other features were noted that would throw light on this particular type of cardiac failure.

Embolism. Embolism, usually involving the lungs and the brain, was a common occurrence, being the cause of death in 3 patients. It was thought to have been present clinically in 3 recovered cases. This complication had its origin not in thrombotic valvular disease, but in mural endocardial thrombi. This was certain in Cases 1 and 2 and most probably so in Case 4, despite the presence in the latter of mitral stenosis and auricular fibrillation. Embolism was present not only in the terminal phase, but was also one of the early developments of cardiac failure as indicated by the occurrence of hemoptysis a few days after delivery in Case 3. Hermann and King[5] noted passive pulmonary infarction, the origin of which they attributed to chronic passive congestion of the lungs and "acute parturient slowing of the movement of the blood mass," secondary to a myocardial degeneration. Our pathologic observations, both gross and histologic, led us likewise to believe that the pulmonary infarctions have their genesis in a weakened and diseased myocardium, but, contrary to the thought of Hermann and King, we feel that the origin of these infarctions is related to embolism: that mural thrombi, as demonstrated in our necropsied cases, are formed within the heart as a result of severe muscle degeneration, which in some cases is comparable in its severity to that seen after acute coronary occlusion, or else they are formed as a result of static thrombus formation in the mural meshwork of dilated auricles and ventricles. This view of the origin of the pulmonary infarctions receives support from the occurrence of the cerebral and other systemic embolisms that were noted so frequently in the same patients.

Histopathology. The histologic changes are unlike those seen in the common forms of myocardial failure. The lesion is focal, but in Case 4 had become remarkably conglomerate and diffuse throughout both ventricles. Two of the hearts showed what may be termed the acute stage of the lesion; a third case showed numerous old lesions and some in the subacute stage; a fourth showed gradation from the chronic to a fairly active subacute stage. The older fibrotic lesions were perhaps best seen in Case 3, where they occasionally occurred in a perivascular location, but more often were scattered indifferently throughout both ventricles independent of vascular relationship. For this reason, we believe that the chronic changes represent a healed focal myocardial lesion of an idiopathic type.

The outstanding feature noted in the acute and subacute phases

appears to be a disintegration of the myocardial fibers involving the nuclei to a lesser extent so that the latter remain as a conspicuous and often major element in the cellular collection that has replaced the myocardium. Hemorrhage into these areas is a rather common finding. A moderate number of lymphocytes and macrophages, occasional neutrophils and also eosinophils (Case 1) are present, but the myocardial nuclei are found in practically every active lesion, indicative of a sarcoplasmic degeneration rather than an interstitial infectious inflammation. They are seen at the periphery of the focus, stranded by the dissolution of their cytoplasm or already adrift, mingling with the cells of the fixed tissue. In some fields these nuclei remain standing in more or less parallel rows, approximately their normal position, but now somewhat more compact, as if they have been compressed by the pressure of the surrounding myocardium. As these lesions become older, they are invaded by fibroblasts, the original myocardial nuclei disappear, and ultimately acellular scars replace the lesion.

Occasionally, two or more nuclei are clumped together in small "giant cell" formation at the periphery of the lesion. They probably represent some attempt at regeneration. The pathologic change is not confined to focal destruction. In many fields the muscle structure is intact, but the fibers show marked degenerative changes, the sarcoplasm apparently being reduced in amount so that the fibers twist or become sacculated, their striations lost, and occasionally they end up in a mass of tangled fibrils. The focal necrosis may represent only an advanced stage, which was originally preceded by a mild diffuse non-necrotic involvement of the muscle. If this be true, it would appear reasonable to believe (this, of course, is hypothetical) that less severe forms of this myocardial degeneration occur not infrequently and eventuate in recovery; whereas, the pathologist will encounter only occasional instances of what apparently, at least from his viewpoint, is an uncommon form of cardiac failure.

The arteries were found to be patulous throughout. The arterioles showed moderate thickening in the scarred areas, but not in the early destructive lesions. The histopathologic changes of neither rheumatic carditis nor lues were present in any case, nor the type that we associate ordinarily with hypertensive heart disease.

The Relationship of Possible Nephritis and Hypertension to Puerperal Heart Failure. The blood-pressure readings in patients (Cases 2 and 3) indicated a mild hypertensive state. The systolic blood pressures ranged between 150 and 160; the diastolic pressures between 90 and 120. Eyeground examination done in 2 patients showed nothing of diagnostic importance. The heart weights in the 4 necropsied cases, 2 of which were known to have had hypertension, showed a definite increase over the normal, ranging from 450 to 500 gm. It is accepted that a heart weight of 450 gm. and over in

the absence of other provocative factors is evidence of idiopathic hypertension, although blood-pressure readings may have been normal or lower by the time the patient came under observation. However, the increase in weight may well have been due to the many degenerative and necrotic lesions throughout the myocardium and to the considerable edema. It is possible, therefore, that hypertension may have been a factor in this unusual cardiac degeneration, but the number of cases studied is entirely too small to permit us to draw any conclusion. Case 1, it is to be noted, definitely did not have hypertension. We wish to emphasize that, in our opinion, hypertension was not responsible as a sole cause for the cardiac lesion. Our reasons for this conclusion are that neither the clinical nor the histologic pictures conformed to those seen in either the malignant or the chronic hypertensive state.

It is almost a matter of tradition to invoke a nephritic factor in severe edematous states in pregnancy and the puerperium. Every one of our patients was regarded as nephritic, either on admission to the hospital or by the private medical attendant. The diagnosis of nephritis has to be supported by laboratory evidence which was practically negative in all cases except for a short interval of toxemia in one of the surviving patients, and in that instance the renal-toxic symptoms quickly abated after delivery. Case 2 had been treated for nephritis since the first attack of decompensation 11 years previous to the final childbirth and eventual cardiac death. Necropsy revealed essentially normal kidneys. There was a moderate arteriolar sclerosis as evidenced by thickening of the small vessels in the spleen, kidney, and to a lesser degree in the myocardium. These findings were in accord with the history of comparatively recent and mild hypertension. In Case 3, there was a small area of necrosis in one kidney, apparently an early septic infarct incidental to the staphylococcus bacteremia. The large majority of the glomeruli and the kidney as a whole presented a normal appearance. The kidneys in Case 1 were normal except for small infarcts and congestion, and in the remaining autopsied case (Case 4), also were normal.

The Relationship to Infection. The finding of a so-called "primary myocarditis" or "myocardial degeneration" in cases of women recently delivered suggested the possibility of a causal influence by focal infection connected with gestation. Investigation from that angle was fruitless. Gynecologic examination was negative, and this was verified in the 4 necropsied cases. One of the women (Case 1) may have had phlegmasia alba dolens for a short time after delivery. However, when she came under our observation, there was no evidence of phlebitis or lymphangitis.

Any case showing obvious pyemia would necessarily be rejected on the supposition that its clinical-pathologic aspect would be ob-

secured. In Case 3, there were two conditions which must be considered before the severe myocardial change that was present could be ascribed to the idiopathic influences of pregnancy and the puerperium: 1, This patient died with a *Staph. aureus* bacteremia, which we believe was a terminal event, resulting from a stubborn bed sore that had developed after 3 months of cardiac decompensation; 2, necropsy also revealed a collection, approximately 30 cc. of inspissated milk and pus behind the right breast which gave neither signs nor symptoms, and was not recognized during life. Microscopically, it was found to be a chronic lesion, probably originating after the patient's miscarriage. We do not see how this lesion, which may conceivably have been infectious, could have been the cause of the myocardial failure; first, because latent encapsulated, clinically quiescent, breast abscesses are by no means rare, and so far as our knowledge goes, have never been associated with myocardial failure; second, heart failure in this instance began before the miscarriage, and presumably, therefore, before the development of the mammary lesion.

The clinical picture and also the gross morbid anatomy in our patients was similar in many ways to that rare form of subacute idiopathic myocarditis occasionally reported under the synonym "Fiedler's myocarditis."[9] The etiology in that disease is thought to be infectious, but in view of the remarkable diversity of disease states that have preceded cardiac involvement, one must conclude that the term "Fiedler's myocarditis" is a little more than a convenient name for myocardial inflammations that do not fall into standard classifications. In the large majority of case reports of isolated idiopathic myocarditis, the authors have stressed the interstitial and apparently distinctly infectious character of the lesion.[1,4] In a few cases there has been an associated parenchymatous involvement with dissolution of the myocardial substance and the appearance of "myogenous" cells,[8] similar in some degree to the histologic picture in our own material, and it is possible that some of the cases of subacute idiopathic myocarditis were identical with those comprising this report. However, as far as we can ascertain, no reference has ever been made to pregnancy or the puerperium as having any bearing on the clinical course or possible etiologic relationship to the lesion.

The Possible Relationship to Thyrotoxicosis. We mention this because of the occasional reference to the possible influence of thyroid disturbance in the "toxic cardiorenal state" of the puerperium.[13] There are also occasional reports of focal myocardial necrosis in the very severe states of thyrotoxicosis.[11] Marked sarcolysis, however, was not featured, nor was embolism noted either in Weller's case or in a patient of our own who showed focal myocardial degeneration associated with advanced toxic goiter.

We considered the possibility of thyrotoxicosis, but since none of the patients showed any sign or symptom suggestive of the disease, and since it was felt that the state of the patients precluded accurate determination, basal metabolism studies were not done on any of the necropsied cases. In 1 recovered case, the basal metabolic rate was + 12%.

Etiology. It is impossible for us to form any definite opinion as to the etiology of this lesion. The majority of these women began to have cardiac embarrassment in the late months of pregnancy. Every case, however, developed it to its most serious degree in the puerperal state, which is opposed to the usual behavior of toxic phenomena in parturient women, since such phenomena ordinarily are quickly terminated by delivery. These facts suggest to us that probably more than one factor may be responsible; that some process in the puerperium may aggravate and prolong whatever cause for cardiac embarrassment existed before confinement. It is reasonable that cardiac muscle made vulnerable by previous disease such as hypertension, rheumatism, or possibly other infection, may be more readily damaged by the unknown puerperal factor than will be the case with normal hearts. Beyond the statement of these few facts, discussion of the etiology becomes hypothetical. The pathologic-physiologic status of pregnancy is very complex, and many diverse possibilities have therefore come to mind, such as calcium deprivation, dietary deficiencies, the action of proteolytic enzymes, and the administration of ergot. Some of these speculations could be dismissed on the basis of the available clinical data, but since we have not been able to subject any of them to the control of detailed clinical research, the solution for the problem remains for future study.

Summary.—1. A clinical study was made of 7 women having cardiac decompensation in the puerperium. Four of these patients died, and at necropsy showed a myocardial degeneration differing from the lesions ordinarily associated with the current classification of heart disease.

2. The coronary arteries were normal and there was no evidence of coronary occlusion in the living patients.

3. Death occurred in 3 cases following embolism, which had its origin on the endocardial surface of degenerated heart muscle. No other proven source of embolism was found.

4. Pulmonary and cerebral embolism were notable. Slight patency of the foramen ovale, apparently due to recent pressure changes within the right auricle and allowing the passage of a pencil was present in one instance. No patency was demonstrated in the 3 remaining cases.

We are indebted to the following chiefs of service: Drs. Riesman, Robertson, Stevens and McGlynn; and to the following pathologists: Drs. Gunn, Fishback, Kennedy and Brody for the privilege of presenting these cases.

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MYOCARDIAL ABSCESS WITH PERFORATION OF THE HEART.

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Abscess of the myocardium is relatively rare. In most instances it is a metastatic manifestation of overwhelming sepsis and is of more theoretical than clinical significance. The literature on the subject is meager. Most of the case reports in the older literature consist in a gross description of the heart without information on the clinical course or bacteriology. Some of these earlier cases described as abscess were undoubtedly necrosing cardiac infarctions.

In the necropsy records of the Department of Pathology of this hospital, abscess of the myocardium was noted in 31 cases, with bacteriologic data available in 26. *S. aureus* sepsis was responsible in 20 cases, pneumococcus in 2, *S. viridans* in 2, *S. pyogenes* in 1, and meningococcus in 1.

Abscess of the myocardium may rarely develop as a solitary local manifestation and lead to perforation of the heart. In the 31 cases in this hospital rupture as a result of the abscess occurred but twice. Both of these cases were observed within 1 year. The primary purpose of this communication is to report these 2 cases, and to cite similar cases found in the literature.

Case Reports. Case 1.—J. H. (No. 803299), a 73-year-old white male laborer, was admitted complaining of shortness of breath for 4 months. For a year he had had some difficulty in urination, occasional incontinence, day and night frequency and had become very thirsty, taking 2 gallons of water daily. Although his appetite had remained good, he had lost 10

pounds. About 4 months prior to entry he began to get weak and dizzy and to have dyspnea on exertion. This increased, and finally he had also several attacks of nocturnal dyspnea in bed. He had had no chest pain and no dependent edema. His past history was irrelevant.

The *examination* revealed an elderly thin man lying quietly in bed in no great distress. The lips were cyanotic. The respiration was Cheyne-Stokes in character. The heart was moderately enlarged; the sounds were distant and of poor quality, and there was a faint blowing aortic diastolic murmur. There were a few moist râles at both lung bases. The abdomen, extremities and reflexes were normal. The temperature was 98.6° F., pulse 120, respirations 20. The blood pressure was 130/60 mm. Hg.

Laboratory studies revealed sugar and a trace of acetone in the urine. The blood hemoglobin was 82%; leukocytes 13,400 per c.mm. (76% neutrophils). The Kahn test of the blood was positive. The non-protein nitrogen was 33 mg., and the fasting blood sugar 95 to 124 mg. per 100 cc. Electrocardiogram revealed sinus rhythm, T_1 inverted, T_2 and T_3 upright with slightly low origin.

Course. The patient was slowly digitalized and the râles disappeared from the lung bases. Since he could not void, an inlying catheter was inserted. His diabetes was regulated by diet and by an occasional dose of 5 units of insulin. The patient was weak, and developed decubitus ulcers, also a cystitis. On the 10th day there was a rise in temperature to 100° F. and acetone again appeared in the urine. Repeated doses of orange juice and 5 units of insulin at 4-hourly intervals cleared this state and the patient seemed better. The next day he suddenly awoke with a severe pain across the costal margins. He went into circulatory collapse, developed severe Cheyne-Stokes' breathing, and died 4 hours later.

Necropsy. The pericardial cavity was markedly distended and filled with about 300 cc. of clotted blood. The visceral pericardium was rough, granular and hemorrhagic. There was a point of rupture of the right ventricle 1.1 cm. in length, anteriorly and 3 cm. to the right of the left coronary and 1 cm. below the base of the pulmonary artery, or just below the tip of the right auricular appendage externally (Fig. 1).

The heart weighed 540 gm. There was moderate increase in pericardial fat. The right auricle and tricuspid valve were normal. The right ventricle was 0.5 cm. thick; its endocardial surface was pale grayish-brown. At a point 0.7 cm. below the base of the pulmonary valve and 2.2 cm. lateral to intraventricular septum there was a point of rupture, its inner orifice being about 0.8 cm. in diameter. Its margins were irregular and frayed with clotted blood adhesions. Over this area the myocardium was pale grayish-brown, and showed a few small, irregular, yellowish points about 0.1 cm. in diameter in a rim about 0.5 cm. wide. The left ventricle was moderately dilated and hypertrophied to 1.9 cm. in thickness. The left coronary artery was widely patent but showed numerous small yellow plaques of sclerosis in the first portion. The right coronary orifice was narrowed to 0.2 cm., but the vessel was patent.

The aorta showed marked diffuse aneurysmal dilatation of arch and thoracic portion, as well as marked diffuse patchy sclerotic thickening. The rest of the examination revealed no relevant findings.

Microscopic Examination. The ventricular wall was normal except over the pericardial surface, where a fibrinous and neutrophilic exudate was present and under which were small foci of lymphocytes. The coronary vessels were well preserved. *Surrounding the ruptured area* there was marked diffuse neutrophilic infiltration of pericardium and myocardium with acute necrosis of the heart muscle. The thrombus in a branch of the coronary artery contained neutrophils, lymphocytes and macrophages.

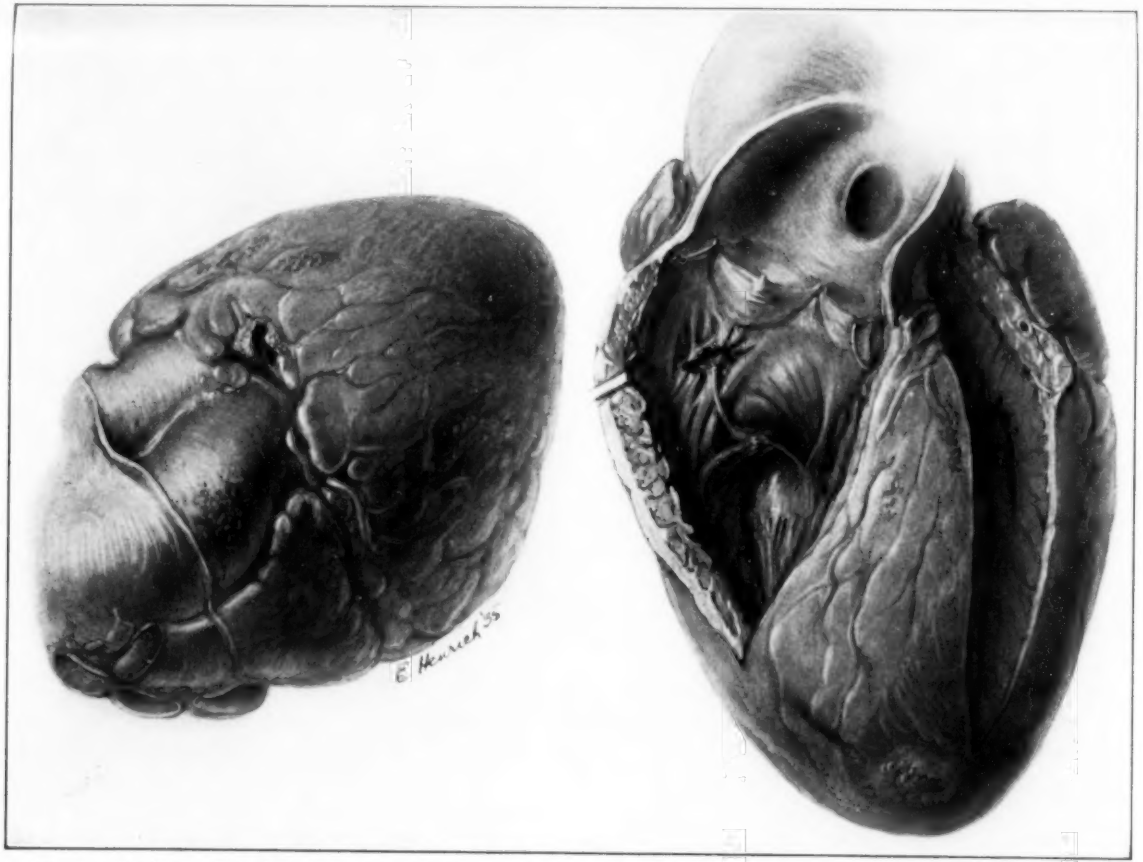

FIG. 1.—Cardiac perforation of *S. aureus* abscess. Pericardial (left) and endocardial (right) appearance of the rupture.

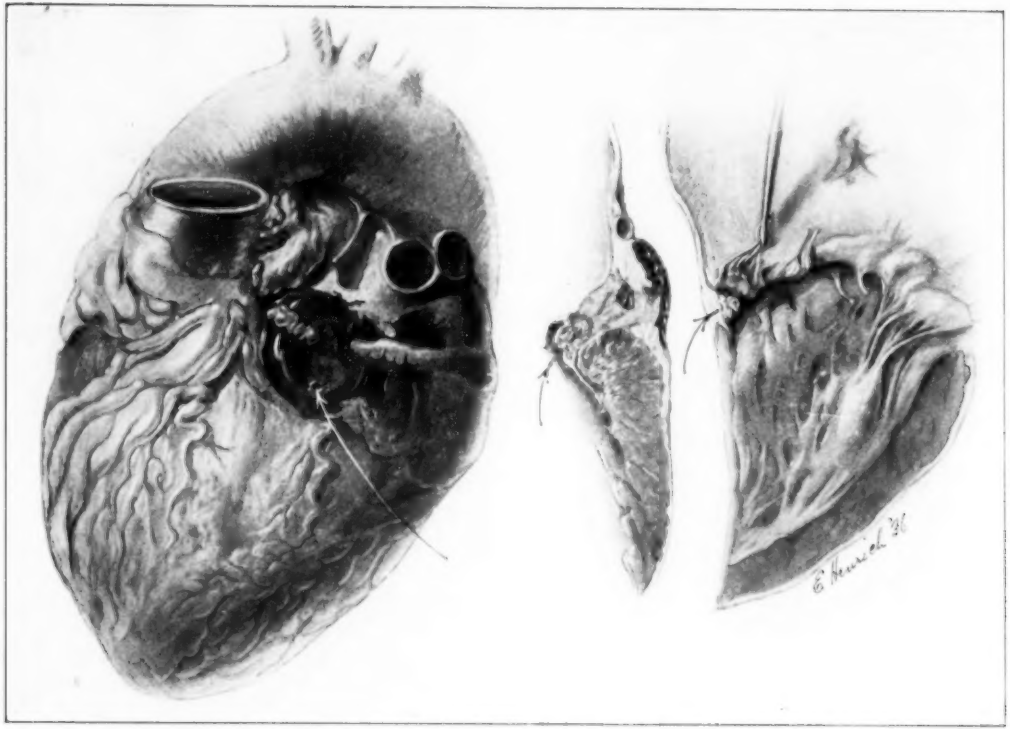

FIG. 2.—Myocardial abscess originating from an extension of a pneumococcus endocardial vegetation. Small pericardial perforation with hemorrhage (left); abscess tract between vegetation and pericardial perforation (center); and location of small vegetation under the mitral leaflet (right).

The Gram-Weigert staining showed numerous Gram-positive cocci in pairs and clusters in the abscess area. Similar cocci were noted in the thrombus and in the pericardium. Bacteriologic examination of the blood obtained from the cardiac cavity yielded a pure culture of *S. aureus*.

CASE 2.—M. McG. (No. 835250), a 78-year-old white woman entered the hospital complaining of an intermittent, throbbing precordial and epigastric pain for 2 weeks. There had been no cough, chills or fever. The past history was irrelevant.

The *examination* revealed an aged, poorly developed, emaciated woman lying quietly in bed and apparently not acutely ill. The heart was enlarged, with the apex impulse in the anterior axillary line. The sounds were forceful, rhythm regular, no murmurs. There were râles at both lung bases and also at the left apex posteriorly, but no dullness. The abdomen, extremities and reflexes were normal. The temperature was 99° F., pulse 110, respirations 25 per minute.

Laboratory Studies. The urine was normal except for 12 to 14 white blood cells in the sediment. The hemoglobin content was 64%, and the white blood count 25,800 per c.mm. (neutrophils 94%). The shape of the red cells and platelets was normal. The Kahn test of the blood was negative. The non-protein nitrogen was 27 mg. per 100 cc. Roentgen ray of the chest showed bronchopneumonia at both bases. An electrocardiogram showed normal sinus rhythm; the rate was 136 per minute, and there was a low origin of *T* in the fifth lead.

Course. There was improvement for the first 2 days in the hospital; the temperature was normal on the second day, although the pulse rose to 125 and the respirations to 35. On the 3d day the patient suddenly went into collapse, with a subnormal temperature and a drop of the pulse rate to 90. There were no new complaints associated with this episode, which terminated fatally in a few hours.

Necropsy revealed a hemopericardium, with the heart completely surrounded by about 150 cc. of blood clot and fluid. The heart weighed 260 gm. On the epicardial surface of the left auricle in the region of the mitral ring was a raised blackish-red area 3 by 4.5 cm. in size, coated with fibrin. A probe could easily be inserted into it (Fig. 2). On section it was seen to consist of necrotic epicardial fat.

In the left ventricle beneath the aortic leaflet of the mitral valve were several very small friable vegetations. In one area a probe could be easily passed upward beneath the valve into the necrotic portion of the epicardium. Microscopic section of this sinus showed blood clot, numerous neutrophils, fibrin and beginning organization. Diplococci were seen in the cytoplasm of some of the leukocytes. Culture of the abscess and also of the endocardial vegetations grew pneumococcus, Type 14. The myocardium, endocardium, papillary muscles and chordæ tendineæ were negative except near the vegetations, where there was edema and some necrosis.

The coronary arteries showed a considerable degree of atherosclerosis and a small branch of the circumflex supplying the abscess area could be traced until its lumen became almost obliterated, with no evidence of rupture.

The right pleural cavity contained 200 cc. of clear amber fluid, and the left 100 cc. The left lung was completely bound down by easily broken adhesions. The right lung weighed 480 gm. and the left 525 . The lower lobes of both lungs were dark in color, subcrepitant, and contained patchy areas of consolidation, particularly the left. On section, purulent yellow material could be expressed from scattered areas over the lower lobes. In the upper part of the left lobe there was an area of consolidation 5 cm. in diameter. The rest of the examination revealed no pertinent findings.

Discussion.—Abscess of the myocardium may rupture either into the cavities of the heart or into the pericardial sac. Howitt,[5] in 1846, reported the postmortem findings on an 8-year-old boy who fell gradually into coma. One may assume that the cause of his ailment was sepsis. The pericardium was distended and a pint of pus was found in the sac. At the juncture of the right auricle and ventricle an abscess was incised containing a teaspoonful of pus. The abscess cavity communicated with the right auricular cavity. No statement is made as to whether the abscess opened into the pericardium. Moxon,[8] in 1869, described the case of a boy aged 11 in Guy's Hospital, who suffered from high fever and delirium. Physical examination of the chest was not made. At postmortem examination turbid fluid was found in the left pleura. There was an acute fibrinous pericarditis. Several small abscesses were located in the myocardium. One of these had ruptured into the left ventricle. Similar abscesses were found in one kidney and in the bones. This was undoubtedly a case of sepsis of undetermined etiology. In 1884, Haddon[4] reported 2 cases of ruptured heart. One of these occurred in a boy, aged 6, who died suddenly while suffering from a disease of septic nature. On postmortem examination, scattered abscesses of the body were found. Severe fibrinous and purulent pericarditis was present. There was a rupture of the left ventricular wall posteriorly, near its junction with the auricle and just below the coronary sinus. This opening led to a small abscess cavity which, in turn, communicated again with the ventricular cavity just below the posterior flap of the mitral valve. Endocarditis was not present. No bacteriologic examination was made. Formad,[3] in 1893, demonstrated a specimen of the heart of a man who died suddenly while diving. In the left ventricular wall posteriorly an abscess, the size of a large bean, was found. The pericardium contained seropurulent fluid. Several ecchymoses were present over the pericardial surface. No mention is made of the rest of the postmortem examination, or of the etiology of the abscess. Rudolf and Moorhouse,[10] in 1916, described the case of a 20-year-old soldier with normal circulatory signs who, while in the hospital with a shrapnel wound, developed a septic state. Subsequently a short systolic "swish" and a marked, rough diastolic bruit could be heard over the second and third costal spaces on the right, close to the sternum. A diastolic thrill was palpated over the same area. Necropsy revealed a pericardial sac containing yellowish fluid with fibrin and a partially resolved blood clot. On the inner wall of the dilated right ventricle, an ulcerated area opened into a narrow channel of an abscess. The latter invaded the interventricular septum, opening again just under the semilunar valve of the aorta. The pericardial wall was intact and the myocardial abscess must have been metastatic. Bacteriologic examination was not made. Stevenson and Marshall,[11] in 1928, described the case of a

boy, aged 9 years, who suffered from a *S. aureus* sepsis and died rather suddenly. Postmortem examination revealed a fibrinous pericarditis. The heart contained three small abscesses. Two of these ruptured into the pericardial cavity and were covered with blood clots. McLagan,[7] in 1928, reported a case of a 57-year-old man who, following a large carbuncle, developed a generalized sepsis. In this illness he developed a "seizure" and collapsed. Postmortem examination revealed the pericardial sac filled with a soft clot. A small probe could be passed into the right coronary artery and into a small cavity containing 1 cm. of pus. Bacteriologic examination was not made.

We were able to find in the literature only these 7 cases of rupture of the heart by abscess described in sufficient detail to rule out other conditions. In 611 cases of spontaneous cardiac rupture collected and analyzed by Krumbhaar and Crowell,[6] abscess was mentioned in only 3 instances. In 92 additional cases of ruptured hearts analyzed by Davenport,[2] 2 were the result of abscess. It is probable, however, that the condition is more frequent than indicated by these reports in the literature.

Abscess of the heart occurs not only in man, but also in animals. Oehl[9] mentions that during the period of 1892 to 1921 he never observed cardiac abscess in cattle, either during meat inspection or in numerous autopsies. During the year 1921 he encountered the condition in 2 instances. The first case was that of a 4-year-old fat cow which, on the day she was butchered, had been driven a distance of 8 kilometers without difficulty. About a hand's breadth above the apex of the heart a bulging and fluctuating area about the size of a plum was found. This "silent" abscess containing creamy pus apparently did not rupture. In the other instance, the cow appeared to be previously in good health and died suddenly during the night. The autopsy revealed an abscess about the size of an egg in the lateral wall of the left ventricle. The musculature in the inside of the heart was of paper thinness and had a perforation about the size of a 10 "pfennig" piece. Dark, loose coagulated blood surrounded this area of perforation into the ventricle. The author believed that these solitary abscesses developed as a result of a cardiac lesion caused by epidemic foot-and-mouth disease, secondarily infected with the Bacillus pyogenes.

The 2 human cases here reported are quite unique in that no other abscesses were found in the body. In the first case, the staphylococcus abscess of the heart probably originated from urinary sepsis; in the second case, the myocardial abscess was a direct extension of a small mural pneumococcus vegetation, a complication of a bronchopneumonia. In the latter case, the abscess was localized in the fat tissue at the junction of the auricle and ventricle. As indicated from other case reports in the literature, abscesses have a certain predilection for this area.

In both of the cases reported by us the small coronary arteries traversing the abscessed area were thrombosed, but the histologic picture of the thrombus indicated that it was a secondary, rather than a primary, process. Abscess of the myocardium may, however, develop as a secondary process in a previously infarcted area caused by a primary coronary thrombosis, as indicated by the remarkable case reported by Cossio and Berconsky.[1] A 64-year-old man suffered for 2 years from manifestations of coronary sclerosis and later thrombosis. Three days before coming to the hospital he developed thoracic pain and respiratory difficulty. During his 2 weeks' stay in the hospital he had fever, signs of bronchopneumonia and leukocytosis, and electrocardiographic changes. Gradually circulatory collapse supervened and he died. Postmortem examination revealed a pneumococcus meningitis and myocardial abscess containing pneumococci. The latter was localized within the old infarcts. One has to assume that the infarcted area was predisposed to the formation of abscess. In support of this assumption, we have observed the formation of pneumococcus abscesses at the site of intramuscular injection of caffein to patients with lobar pneumonia.

The clinical manifestations of myocardial abscess with rupture, as judged from the 7 cases in the literature and the 2 cases here reported, are variable. The abscess itself is usually symptomless until its rupture causes sudden precordial non-radiating pain followed by progressive circulatory collapse (pericardial tamponade) causing death within a few hours. The case of Rudolf and Moorhouse[10] indicates, however, that the dissection of the myocardium by an abscessed tract can be responsible for systolic "swish" and rough diastolic bruit. The diastolic murmur heard in Case 1 may also have been caused by the opening of the abscess into the ventricle. The electrocardiogram, as indicated by the 2 cases here reported, may be essentially normal before the rupture of the abscess. It is of interest that none of the reported cases of cardiac rupture due to abscess has been diagnosed clinically.

Summary. 1. Two cases of solitary myocardial abscess with perforation of the heart are described. In the first case the abscess, caused by *S. aureus*, ruptured into the right ventricle as well as into the pericardial sac. In the second case the abscess, caused by pneumococcus, was localized mainly in the fat tissue at the junction of the auricle and ventricle and was formed as a direct extension of a small mural pneumococcus vegetation. This abscess ruptured into the pericardial sac. In both cases the clinical course did not suggest sepsis and the unexpected cardiac perforation resulted in a fatal circulatory collapse.

2. While abscess of the myocardium in cases of sepsis is not an unusual occurrence, perforation of the heart by abscess is rare. Seven such instances, collected from the literature, are cited. As

judged from the 9 cases now available, myocardial abscesses are silent until their rupture causes sudden low thoracic pain, followed by circulatory collapse. In 2 of the 9 cases a diastolic murmur was present.

We wish to thank Dr. Joseph E. Hallisey for granting permission to include the clinical abstract of Case 2.

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THE RÔLE OF DISTENTION IN THE GENESIS OF ACUTE INFLAMMATION OF HOLLOW VISCERA.

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The thesis that acute inflammatory changes may develop as a result of mechanical distention of a hollow viscus will be elaborated on in this paper. It is our impression that bacteria play a subordinate rôle in these changes and are of importance mainly in the stimulation of fluid extravasation which augments the distention factor. It is realized that this concept is in conflict with the current teachings of pathologists, but it is hoped that sufficient evidence can be adduced to lend some credence to the view.

Many of the hollow viscera of the body contain a more or less rich bacterial flora[14,15] and this fact is responsible for the teleologic reasoning which assumes that if bacteria are found in pathologic tissues they must have an etiologic relationship. If the organ, ordinarily sterile, is found to contain bacteria and to show pathologic changes, such reasoning is acceptable. In the case of the appendix, for example, which is a tube containing many types of organisms, Wangensteen and Bowers[24] have shown that relatively few cases of acute inflammation show organisms in the tissues but that incidence of organisms is increased if gangrene has supervened. In this case, since the bacteria tend to appear late or not at all in the course of the disease, they cannot be assumed logically to play the important etiologic rôle. That the absorption of bacterial products is not always a factor in the production of acute inflammatory changes in an obstructed hollow viscus will be shown later.

Van Zwalenburg,[23a,b,c,d] in his excellent papers, describes the sequence of events which leads to acute inflammation in a distended

hollow viscus, in which the lumen is obstructed. The arteries at systolic pressure carry fluid into the viscus, which is drained at a much lower pressure by the veins and lymphatics. There is fluid in the lumen, having a greater osmotic pressure than the tissue fluids. Consequently there is a shift of fluid from the vessels and tissues into the lumen, thus initiating the distention factor. Small venules become occluded and serum begins to be extravasated. As distention progresses, veins and lymphatics become further blocked by pressure within the lumen and as the blood flow is decreased, diapedesis of leukocytes begins. On the aspect of the organ opposite to that into which the vessels enter, blood supply is poorest and here the flow is first entirely blocked. The arteries continue to pump in blood and now the small venules and capillaries rupture. The tissues are now deprived of oxygen and necrosis begins. On the side opposite to the origin of blood supply, small diamond-shaped infarcts develop and finally rupture occurs through these sites. Bacteria may or may not enter the dead tissues, but, as can be seen from Van Zwalenburg's description, they are not essential. They may augment the changes which already have been initiated.

Van Beuren[22] describes this same mechanism as that by which perforation is induced in cases of intestinal obstruction. This sequence of events seems to be well accepted in the case of intestinal obstruction but apparently this knowledge has not been applied in the study of pathogenesis of similar conditions.

Infiltration of tissues by neutrophils is generally credited to bacterial invasion, but this is not necessarily the case. Pepper and Farley[16] state that broken-down tissue in small amounts, may give a marked and early rise in white count. Downey[8] feels that even in the case of acute appendicitis, there is enough tissue damage to explain the very early leukocytosis. Prochnow[19] showed that leukocytosis with relative increase in neutrophils could be demonstrated postoperatively, even in non-infected herniaplasties. This shows that tissue damage may be responsible and infection need not be present. According to the descriptions of Van Zwalenburg and Van Beuren, it is easy to see that tissue death is not a late event in the chain.

That slowing of the blood stream is accompanied by extravasation of fluid into the tissues is so well recognized that arguments and examples need not be cited. Van Zwalenburg[23a] distended intestinal loops and found that as the blood supply was obstructed, even in a dry atmosphere, drops of fluid appeared on the serosal surface. Downey has shown that venous stasis will cause leukocytic infiltration of tissues, consequently, necrosis of tissues need not precede accumulation of leukocytes.

These inflammatory changes do not follow upon the slow increase in size of a cyst, because the blood supply has an opportunity to accommodate itself to the slowly increasing distention. This is

illustrated in such cases as mucocele of the appendix, where great distention may be present without inflammatory changes.

From the foregoing discussion, it would seem that acute distention of an obstructed hollow viscus is followed by acute inflammatory changes. It remains now to show that this can be demonstrated experimentally.

Material and Method. In the experimental work, dogs were used. The tissue specimens were fixed in formalin and sections stained with hematoxylin and eosin or with Gram-Weigert for bacteria. Smears and cultures were made of tissues and lumen content. Where constant pressure was applied within the lumen of a hollow viscus, the Perusse bottle was used. This apparatus is so arranged as to deliver a constant but adjustable water or air pressure. In some experiments, increased intraluminal pressure was induced by filling the obstructed or normally closed lumen with sterile hypertonic saline or glucose solution.

I. *Clinical Material.* Within the past few years, several investigators, including Andrews[1] and Westphal,[25] have implicated mechanical factors as etiologic agents in appendicitis[4] and gall-bladder disease. Andrews feels that stones are precipitated by biliary stasis and that once stones begin to form, the pressure-distention mechanism is in full swing. Westphal, in a paper on appendicitis, likens the appendix trying to expel a fecalith to the gall bladder attempting to expel a calculus. He feels that both conditions are in reality dependent on a pressure mechanism. The cystic duct is usually found to be plugged by a stone in cases of acute cholecystitis. This observation is borne out in an unpublished series of cases studied by Zierold.[27]

1. *Clinical Appendicitis.* The thesis that acute appendicitis is usually a form of closed loop obstruction rather than a bacterial disease is now being made the subject of an extensive investigation. Though the data cannot yet be published, some of the conclusions reached thus far will be indicated. In 108 cases of appendicitis studied at the Minneapolis General Hospital in 1935, there was an 81% incidence of definite obstruction to the lumen in the acute cases, caused by an impacted fecalith in 60% of the cases. In the perforated cases, the incidence of obstruction rose to 97% and a fecalith was the obstructing mechanism in 81%. These appendices had the pathologic characteristics of closed loop obstruction with all inflammation distal to the point of obstruction. There was marked distention with thinning of the walls and the perforations routinely appeared on the antimesenteric side. Correlated with these findings are the observations that bacteria were found in the tissues in only 12% of the non-gangrenous appendices. In the gangrenous and perforated group, the incidence of bacteria in the tissues rose to 17%. These preliminary reports tend to confirm the impression that the obstructive element is very important and the bacterial element of lesser significance. These results check closely with a

large experimental series and a clinical series from the University Hospital.

That the obstructive mechanism may be of great importance in the causation of appendicitis is not a recent idea and was advocated in 1897 by Pozzi,[18] who accredits the original idea to Dieulafoy. Pozzi stressed the importance of the valve of Gerlach as a factor in converting the appendix into a closed loop. This factor is being investigated by Wangensteen and his coworkers, who find evidence of a sphincter-like mechanism at the base of the appendix. Considerable resistance to the flow of water is almost invariably encountered, pressures of 30 to 60 cm. of water being withstood before water will run into the cecum from the appendix. Such intraluminal pressures, if maintained over a period of hours, will obviously lead to changes in the appendical wall.

Westphal has shown that two other factors operate to convert the appendix into a closed loop. He has demonstrated that the appendical lumen is normally narrower at the base. Thus, fecal masses, laminated by successive layers of secretion, become impacted at the base. The other factor is that the musculature of the appendix is normally heaviest toward the base. He shows by Roentgen ray examinations that appendical peristalsis is ineffectual in the organ, most often beginning at the base and progressing toward the tip.

Banks and Green[3] report a case of carcinoma of the cecum in which appendicitis developed. At operation the tumor was found to be obstructing the base of the appendix which was inflamed and distended to the size of a banana. They refer to similar cases reported by Mayer, Shears and Parker and Rosenthal.

2. *Carcinoma of the Sigmoid with Perforation of the Cecum.* In support of the idea that a pressure-distention mechanism is capable of causing intestinal perforation, the following similar cases are briefly outlined. Both patients were elderly men with carcinoma of the sigmoid colon. Each had been given barium by mouth and then was sent to the hospital with a diagnosis of intestinal obstruction of unknown origin. The obstruction was complete in each case and Roentgen rays showed tremendous gaseous distention of the large bowel, especially in the region of the cecum. Both patients expired before operative intervention could be made. In each case, at autopsy, the cecum showed multiple perforations through infarcted areas on the side opposite to the entering blood supply.

The ileocecal valve had remained competent, so that with the obstructing carcinoma the large bowel had become a closed loop. As material accumulated and decomposition continued, the distention became progressively greater. The cecum gradually became deprived of its blood supply by increasing intraluminal pressure. Finally, areas of necrosis appeared and through these infarcts, perforations resulted. The tissues showed a severe inflammatory reaction with dense leukocytic infiltration and areas of necrosis,

FIG. 1.—A clinically gangrenous appendix which illustrates the principles of closed loop obstruction, with distention, thinning and gangrene of the walls, distal to the impacted fecalith. The mucosa is ulcerated and sloughing, while the dilated lumen contains dissolving fecalith, fluid and débris. Proximal to the point of obstruction, the lumen is normal in caliber, the wall is normal in thickness and sections show very slight inflammation. Distally, sections show necrosis with thrombosis of vessels.

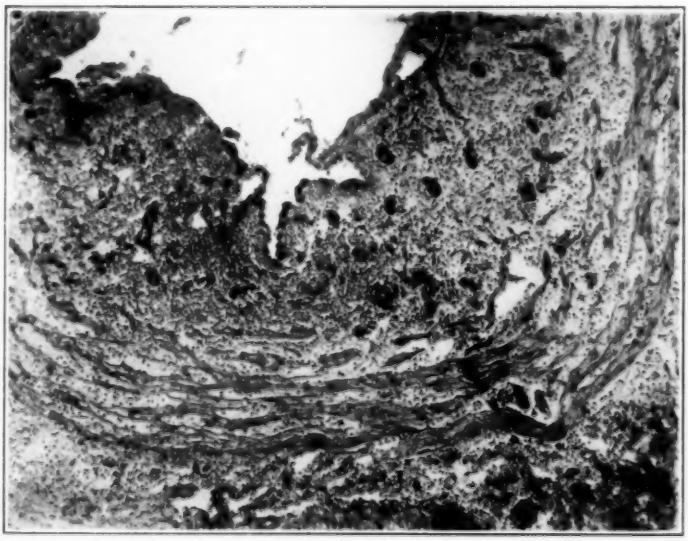

FIG. 2.—Photomicrograph of a dog's ureter after having been subjected to 15 cm. of water pressure for 18 hours. There is edema of the periureteral tissues, marked leukocytic infiltration of all layers, separation of the muscle bundles by distention and inflammatory exudate. The mucosa is necrotic and sloughing. This corresponds closely to the microscopic picture of gangrenous appendicitis.

Gram-Weigert stains showed bacteria on the serosal surface, from the escaped contents but there were no bacteria in the tissues.

Sperling,[21a] in his paper on competency of the ileocecal sphincter, reports 2 cases in which perforation of the large bowel occurred proximal to the point of obstruction caused by a carcinoma. Koucky[13] reports a similar case seen at autopsy and the author has operated upon such a case. This "circumscribed meteorism" was first described by Maydl[20] in 1883 and Bayer[20] in 1889, in which the cecum becomes distended after distal colon obstruction. The development of this phenomenon depends on competency of the ileocecal valve. Kocher[12] in 1889 emphasized that gas pressure in the bowel could cause gangrene and Anschutz[20] and von Greyerz[20] showed that the thinness of the wall and the relative width of the cecum are the causes of the greater distention in this region. The latter inflated two rubber balloons of unequal size, tied to a T tube, and showed that the larger balloon inflated quickly and burst before the smaller one reached any noteworthy size. In this regard De Quervain[20] says, "With membranes of equal elasticity, the pressure is higher when the radius is smaller; therefore, that degree of pressure which will suffice to distend the membrane with the larger diameter, will not suffice for the smaller." Rost[20] states that if air is blown into the rectum, patients first complain of pain in the cecum. Von Greyerz and Shimodeira[20] have shown that distention of the bowel decreases its arterial blood supply. Gatch, Trusler and Ayers[10] have measured the blood flow through obstructed loops distended by various gas pressures and found that as the pressure was increased, the blood flow decreased. They repeated the observation that the greatest effect is seen on the antimesenteric surface. Dragstedt, Lang and Millet[9] concluded that distention interferes with the flow of blood in the vessels of the walls of the intestine.

II. *Experimental Data.* In order to understand the pathogenesis of perforation in obstruction, it is necessary to recognize certain fundamentals in bowel physiology. It is known that the normal sustained intraintestinal pressure in dogs is 2 to 4 cm. of water. There are normally 10 to 12 contractions per minute. Sperling[21b] has shown that simple obstruction doubles the normal intraluminal pressure and with activity of the bowel, this pressure is increased 15 times. He found that a maintained higher pressure gave rhythmic contractions of the same rate but more vigorous in amplitude. The stasis of obstruction not only increases the height of contractions but pyramids the pressure. As the obstructed bowel becomes fatigued, there are intermittent cycles of activity and this explains the colicky type of pain. Sperling also found distention to be an intense stimulus to secretion. This is stressed by Herrin and Meek.[11] These observations bear out the ideas of Van Zwalenburg on the hydraulic vicious cycle. As the fluid pressure increases,

peristaltic and secretory stimulation becomes more intense and this again increases the pressure. Marked changes in absorption also are shown in the obstructed bowel. Sperling demonstrated that absorption is increased up to 40 cm. of water pressure and then decreases. The normal non-distended bowel absorbs 86% of the water placed in it in 1 hour, whereas the obstructed bowel absorbs only 8 to 10%. As the blood supply is cut off by distention, edema occurs and a segment of obstructed bowel increases its weight by 114% in 24 hours, according to Sperling.

1. *Closed Loop Intestinal Obstruction.* In 7 dogs the appendix was severed from the cecum and converted into a closed loop. Some of these loops were full of feces, some empty of gross fecal material and some were washed out with tap water. The specimens were removed at intervals varying from 2 hours to 6 weeks. The empty loops developed acute inflammatory changes only if distention supervened. Both full loops became gangrenous in 48 hours and one perforated. The washed loop, removed after 6 weeks was quite normal. Here we see that, with the same bacteria in all, acute changes were found only when the loop became distended.

In 4 dogs, washed closed loops of ileum were prepared. These were removed in 24 to 72 hours. The early specimens showed marked distention with a hemorrhagic fluid and the 72-hour specimen perforated distally on the antimesenteric border.

In 4 dogs, closed loops of cecum were established. Two were washed and two were full. One full loop perforated in 24 hours and the other was distended and gangrenous in 48 hours. One washed loop was incorrectly prepared, a piece of ileum being incorporated so that it perforated from distention by ileal fluid in 2 weeks. The other washed loop was removed after 6 weeks and was quite distended by gas and fluid but was microscopically normal, probably because the distention had been gradual.

In 2 dogs, closed loops of rectum were made, one full and one empty. The full loop became distended and ruptured the sutures in 5 days; whereas after 6 weeks the empty loop, although distended by gas, was microscopically normal.

From these experiments, several general conclusions can be drawn. 1, the fate of a closed loop is definitely correlated with its location and the function of that segment of bowel. Closed loops of secretory segments regularly distend and rupture whereas absorptive segments become slowly distended by gas and mucus or may remain collapsed. 2, the content of the loop is important in determining the outcome. The contents may act as a hydrophilic agent and cause distention with perforation as will be shown subsequently. 3, the presence of bacteria may cause distention and rupture if they produce fluid and gas by action on the content of the loop. 4, any material in the loop acts as a secretory stimulant. This secretion then augments distention and a vicious cycle is established.

It is seen from these conclusions that bacterial invasion probably is purely secondary to mechanical factors. That the absorption of bacterial products is usually of little significance is shown from the fact that non-distended closed loops show no inflammatory

changes although the lumina contain myriads of living organisms of the same type as those found in distended loops which regularly develop inflammatory changes. Burget, Martzloff, Suckow and Thornton,[5,6] working with jejunal loops, found that daily aspiration of the loop content allowed the dogs to live indefinitely but without aspiration the loops regularly became distended, gangrenous and perforated. They feel that the organisms in the lumen directly or indirectly cause the formation of fluid. Sperling found that the pressures developed in closed loops may be 20 times the normal. Jejunal loops had 7 times the pressure of ileal loops due to more secretion and showed a consequently greater tendency to perforate. Wilkie[26a,b] has demonstrated that ileal closed loops containing carbohydrate material routinely perforate but those containing protein material perforate much earlier due to the more active fermentation, liquefaction and gas production. These changes depend on bacterial action but do not indicate a bacterial origin of the perforation.

2. *Experimental Appendicitis.* Wangensteen and Bowers[24] have shown that distention seems to be the most important factor in the production of experimental appendicitis. In their pressure experiments, using the Perusse[17] bottle, they routinely obtained acute inflammatory changes, applying pressures ranging from 3 to 30 cm. of water and air for 6 to 18 hours. There was a direct correlation between the degree of pressure and the severity of change; also between the length of time applied and the severity. The incidence of bacteria in the deeper tissue layers also showed a positive correlation with the time and degree of pressure.

It has been generally accepted that appendicitis is caused by increase in virulence of organisms due to stasis in the lumen.[2]

The following experiments were carried out to test this idea. In 6 dogs, the appendix was washed clean with tap water and then converted into a closed loop distended with brain broth, gelatine, agar, potato, plain broth and Ringer's solution. This should have given the organisms ample opportunity to increase in numbers and virulence without hindrance. These loops were removed after 1 and 2 weeks. In each instance most of the medium had been absorbed. On smear, the lumina contained myriads of organisms of all types. On section, all these appendices showed a subsiding inflammation. On Gram stain, in no instance were there bacteria in the tissues. Since no bacteria were found in the tissues, it was thought that possibly the inflammatory change was on the basis of distention due to hydraulic imbalance. This was investigated as follows. A dog's appendix was converted into a washed closed loop containing a saturated solution of sodium chloride. In 48 hours the entire loop was gangrenous and showed multiple perforations. This experiment was repeated using concentrated glucose with identical results. It was noticed that very few organisms were present and the experiment was repeated but with the addition of gentian violet to the salt and glucose solutions for any bacteriostatic action which it might exert. These appendices were removed in 24 hours and the loops were found to be gangrenous and covered by a fibrinous exudate. The loops contained 5 times as much fluid as was originally injected. In the

loop containing salt and gentian violet there were very rare organisms, while in the loop containing glucose and gentian violet the contents were actually sterile on smear and culture in liver-peptone broth. None of these tissues contained bacteria on staining by the Gram-Weigert method.

These experiments clearly demonstrate that the osmotic pressure may be of more importance than bacteria in causing gangrene and perforation.

Van Zwalenburg[23a] in 1904 stated that the evident interference with blood supply in appendicitis is best accounted for on the basis of increased intraluminal pressure.

3. *Distention of the Ureter and Renal Pelvis.* The normal upper urinary tract is conceded to be sterile and for this reason it was selected as a suitable site for experiments in acute distention.

In 6 dogs, the peritoneal cavity was opened aseptically and the right ureter was isolated. The ureter was cannulated 6 cm. below the kidney, the cannula pointing toward the renal pelvis. The cannula was then connected to the Perusse bottle. In 2 dogs a pressure of 15 cm. of water was maintained for 6 hours and in 2 others for 18 hours. In 1 dog a pressure of 30 cm. of water was maintained for 6 hours and in another for 18 hours. Only 2 specimens need be described in detail. Fifteen cm. of water pressure for 6 hours produced early gangrenous changes in the kidney pelvis and ureter. Hematuria developed after 2 hours of pressure. The urine was sterile and the tissues showed no bacteria after Gram stain. Water pressure (15 cm.) for 18 hours gave gangrene of the ureter and renal pelvis. Here the picture resembled that of appendicitis, with edema of the periureteral tissues, congestion and hemorrhage in the submucosa, sloughing of the mucosa and dense leukocytic infiltration of all layers. The muscle bundles were pulled apart by the distention and the inflammatory exudate. The urine was sterile and the tissues failed to show the presence of bacteria on Gram stain. This series, while small, shows definitely that acute inflammatory changes may be induced in the sterile ureter and kidney pelvis by increasing the intraluminal pressure. These experiments have no bearing on acute pyelitis nor is it intended to infer that pyelitis is a distention phenomenon (Fig. 2).

4. *Distention of the Urinary Bladder.* The urethra of a male dog was ligated and 500 cc. of Ringer's solution were injected subcutaneously to insure bladder distention. After 24 hours the urinary bladder was tremendously distended, very thin walled and the tissues were so dark as to appear gangrenous. The urine was cultured in liver-peptone broth which after 72 hours showed a sparse growth of Gram positive spore-forming rods. On section, there was relatively little hemorrhage but all of the tissue planes were densely packed with neutrophils. A Gram stain of the tissues failed to reveal the presence of bacteria in the bladder wall.

Creevy,[7a,b,c] in his work on bladder distention, showed that inflammatory changes regularly followed but hemorrhage was a more pronounced part of the picture in his series. In all of his cases of simple urethral obstruction, the urine remained sterile although acute inflammatory changes accompanied the distention.

5. *Acute Experimental Glaucoma.* The effect of increasing the intraocular tension in dogs by the injection of saline into the globe was investigated as follows, all of the preparations remaining sterile.

In 1 animal the anterior chamber fluid was replaced by sterile normal saline solution, under no increased pressure. The eye was removed after 6 hours and was found to be normal on section. In another eye, the anterior chamber was distended with normal saline for a 6-hour period. Sections showed a dense leukocytic infiltration around the vessels at the angle of the iris and choroid coat. Distention of the anterior and posterior chambers by sterile hypertonic saline for 15 minutes failed to produce inflammatory changes. Distention of the anterior and posterior chambers with hypertonic saline for 6 hours, however, produced dense leukocytic infiltration in the vascular areas of the uveal tract. Similar distention for 24 hours produced the same changes but of a more severe character.

In this series it has been shown that normal saline under no pressure, gives no changes, whereas, by injecting about 1 cc. of saline for the same period, the pressure is increased to a point where inflammatory changes develop. Hypertonic saline caused no changes in 15 minutes but gave a progressively more severe reaction as the experiment was carried on for a longer period and its hydrophilic action was exerted. In no case were bacteria present in these specimens.

Conclusions. 1. The thesis that acute inflammatory changes may develop as a result of mechanical distention of a hollow viscus has been postulated and evidence presented to support it.

2. The sequence of events in the development of acute inflammation has been presented from the standpoint of pathologic physiology.

3. Acute cholecystitis may be based on a pressure-distention mechanism.

4. Our evidence indicates that acute appendicitis is a form of closed loop obstruction in the majority of cases.

5. Two cases of carcinoma of the sigmoid colon with gangrene and perforation of the cecum due to gaseous distention and similar cases have been briefly cited in support of the distention thesis.

6. Experiments on closed loop intestinal obstruction indicate that distention is the important factor in the causation of gangrene and perforation.

7. The importance of the hydraulic vicious cycle in experimental appendicitis has been demonstrated.

8. Experimental maintenance of a constant increased intraluminal pressure will cause acute inflammatory changes in the sterile ureter and kidney pelvis.

9. Severe distention of the urinary bladder of the dog results in acute inflammation.

10. The inflammatory changes of acute experimental glaucoma may be induced by osmotic imbalance.

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THE METABOLISM OF NEPHRECTOMIZED DOGS.

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In order to have a basis for the interpretation of the specific dynamic action of glycine in the nephrectomized dog, it was first necessary to have more complete information on the metabolism of the nephrectomized dog. We believe that by limiting our observations to the first 5 to 6 hours after kidney removal, we have a basis for indirect calculation of the energy production of the kidney, uncomplicated by many of the effects which come about by later accumulation of metabolic end products.

It is generally agreed by those who have made direct measurements of the oxygen consumption of the kidney, that its metabolism is subject to wide variations. (Barcroft and Brodie,[1a,b] Fee and Hemingway,[5] Hayman and Schmidt,[7] Van Slyke, Rhoads, Hiller and Alving.[10])

Tangl[9a] found in 9 dogs that the net decrease in energy metabolism ranged from 3.8 to 14.9% with an average of 8.7%. The R-Q rose from 0.808 to 0.837. His dogs were curarized. Later,[9b]

using rats, he found by direct calorimetry, a decrease of 8.2%. St. Cserna and Kelemen[3] observed a decrease of about 8% in normal animals and in experimental nephritis about 12%. After complete nephrectomy, Dock[4] found that nephrectomy resulted in an average decrease of about 5% in energy metabolism.

Experimental. All the dogs used were female mongrels, previously fed on a diet of kitchen scraps, and all were fasted 24 hours previous to the experiment.

In most cases a blood sample was taken before the administration of sodium amytal, which was then given intraperitoneally (60 mg. per kg. of body weight). Eight to 10 minutes usually sufficed for complete anesthetization. Small additional doses (50 to 100 mg. per dog) of sodium amytal were sometimes given intravenously whenever needed to preserve the same degree of deep anesthesia.

As soon as the dog was well asleep a catheter was inserted into the bladder, washing carried out and sample discarded. The catheter was left in place until the bladder was again washed just before nephrectomy (2 to 3 hours). The exact time of collection was recorded and sample saved for analysis.

A tracheal cannula was inserted and connected to a Tissot spirometer. Three 30-minute samples of expired air were collected as nearly continuously as possible before nephrectomy and 5 hourly samples were collected after nephrectomy (Series I). In Series II, only 3 samples covering the first 2 hours after nephrectomy were obtained.

Three blood samples, from either the saphenous or external jugular vein, were collected before nephrectomy; the first, before sodium amytal was given; the second, about 1½ hours later; and the third just before the operation. Five consecutive hourly samples were collected following nephrectomy.

Bilateral nephrectomy was performed through an anterior midline incision and the total time consumed varied from 4 to 15 minutes. All precautions to prevent unnecessary trauma and hemorrhage were observed.

Expired air samples were analyzed by means of an accurate Haldane apparatus. The analyses were carefully checked. Heat production was calculated on total R-Q since protein metabolism could not be measured after extirpation of the kidneys. Blood and urine urea nitrogen determinations were made by the method of Meyers.[8]

The dogs used in Series II were treated in the same way except their metabolism was followed for only 2 hours following nephrectomy. The 5 control dogs were subjected to the same operation except the kidneys were not removed.

Results. The results of a typical experiment are shown in Table 1. It happens in this case that the sodium amytal was given intravenously in contrast to all other experiments where it was given intraperitoneally. The results are no different. We wish to call attention to the constancy of the basal metabolic determinations, under sodium amytal, both before and after nephrectomy. Urea nitrogen accumulates in the blood, after nephrectomy, at a uniform and constant rate.

Table 2 shows the summarized results on the dogs of Series I at the end of 2 hours after nephrectomy. In order to condense the table somewhat, the blood-urea figures are omitted. The decrease in basal metabolic rate varies from 7.21 to 25.98% of the total

metabolism with an average of 15.17%. In the control animals, treated in the same way except that the kidneys were not removed, the range is from 4.84 to 15.31% with an average of 8.94%. This

TABLE 1.—A TYPICAL EXPERIMENT.

July 10, 1935. Dog. 7. Weight, 7.3 kg.
Sodium amytal intravenously: 8:10, 3.5 cc.; 8:40, 1 cc.; 10:10, 0.5 cc.

		Urine urea N per hr., mg.	Blood urea N, mg. %.			
10:10	Bladder washed			10:38–11:08	30′ sample air	13.15 Cal./hr.
12:20	Bladder washed			11:12–11:42	30′ sample air	13.00 Cal./hr.
12:25	. . . . .	213.8	14.1	11:46–12:16	30′ sample air	13.02 Cal./hr.
12:30	Nephrectomy					
12:43	Kidney wt., 38 gm.					
2:05	. . . . .		18.8	1:00–2:00	60′ sample air	11.55 Cal./hr.
3:05	. . . . .		19.3	2:10–3:00	50′ sample air	10.90 Cal./hr.
4:08	. . . . .		20.2	3:08–4:00	52′ sample air	10.97 Cal./hr.
5:05	. . . . .		23.4	4:11–5:00	49′ sample air	10.60 Cal./hr.
6:15	. . . . .		25.2	5:09–6:09	60′ sample air	11.15 Cal./hr.

TABLE 2.—METABOLISM OF NEPHRECTOMIZED DOGS—SERIES I.

Dog No.	Date.	Wt. of dog, kg.	Average B.M.R. per hr.	Average basal R-Q.	Wt. of kidneys, gm.	Average B.M.R. after nephrec., 2 hrs.	Decrease, %.	Decrease per gm., kidney per hr., Calories.
6	7/3	8.2	15.34	.856	42	12.42	19.0	.070
7	7/10	7.3	13.06	.753	38	11.22	14.1	.048
8	7/12	7.7	12.98	.769	41	10.81	16.8	.053
9	7/16	9.5	18.99	.687	60	16.28	14.3	.045
14	9/6	5.5	10.97	.748	31	9.77	10.9	.038
15	9/9	5.9	13.26	.725	32	10.88	17.9	.075
16	9/16	5.9	13.42	.793	38	10.98	18.2	.064
17	9/18	5.5	9.82	.747	34	9.09	7.4	.021
18	9/20	6.6	13.25	.779	37	12.23	7.7	.028
19	9/23	7.3	13.67	.758	38	11.03	19.3	.070
20	9/27	9.5	18.70	.719	52	15.25	18.4	.066
23	10/7	9.0	15.27	.686	55	11.15	26.0	.075
24	10/11	6.8	14.15	.746	37	13.12	7.2	.028
25	10/14	5.7	12.85	.744	41	11.03	14.2	.044
Av.				.751			15.2	.052
			Controls—Laparotomy Only.					
10	7/18	4.5	11.78	.792	36	10.91	7.38	.024
11	7/25	9.1	18.92	.809	..	16.83	11.10	
12	7/30	6.4	11.55	.754	34	10.99	4.84	.015
13	8/1	7.0	9.92	.771	42	9.32	6.05	.014
26	10/15	9.1	12.67	.862	38	10.73	15.31	.051
Av.				.798			8.94	.026

gives an average net decrease of 6.13%. The decrease expressed in Calories per gram of kidney per hour varies from 0.021 to 0.075 in the nephrectomized dogs and from 0.014 to 0.051 in the control dogs.

Table 3 is really a continuation of Table 2 and is arranged in this manner only to conserve space. In every experiment, except that on Dog 24, the *R–Q* rose. This, we believe to be due to the gradual accumulation of non-volatile acidic substances in the blood and tissues following nephrectomy. The decrease in heat production, expressed both in terms of percentage of the total metabolism and in terms of kidney weight, is somewhat less. This is shown also in the control animals and we believe it to be due to the lesser influence of trauma when studied over the longer period.

TABLE 3.—METABOLISM OF NEPHRECTOMIZED DOGS—SERIES I.

Dog No.	Average of B.M.R. for 5 hrs. after nephrec.	R-Q av. for 5 hrs. after nephrec.	Decrease, %.	Decrease per gm., kidney per hr., Calories.	Blood urea N before nephrec.	Blood urea N at end of 5 hrs.	Urine urea N per hr.
6	13.27	.891	13.5	.049	9.5	16.8	34.7
7	11.03	.849	15.5	.053	14.1	25.2	213.8
8	10.81	.819	16.8	.053	23.8	32.9	229.8
9	17.00	.741	10.5	.033	11.2	19.7	266.5
14	9.83	.819	10.4	.037	10.5	27.3	83.1
15	10.93	.788	17.6	.073	13.6	28.1	93.6
16	11.51	.819	14.2	.050	14.7	19.0	87.8
17	9.42	.816	4.1	.012	25.1	41.0	111.9
18	12.52	.844	5.5	.020	17.6	41.6	106.6
19	11.11	.823	18.7	.067	16.4	27.4	66.3
20	15.80	.758	15.5	.056	8.5	18.8	115.8
23	12.30	.790	19.4	.054	7.3	17.5	44.0
24	12.81	.741	9.5	.036	13.4	27.9	70.2
25	11.24	.771	12.2	.038	9.1	22.5	102.8
Av.		.805	13.1	.045	13.9	26.1	
			Controls—Laparotomy Only.				
10	10.82	.823	8.1	.027	20.6	22.5	302.6
11	17.23	.743	8.9	....	25.5	17.9	224.7
12	11.10	.832	3.9	.013	13.4	25.3	98.4
13	9.79	.786	1.3	.003	15.8	14.6	36.8
26	11.85	.823	6.5	.019	10.4	11.9	39.4
Av.		.801	5.8	.016			

The blood urea nitrogen is practically doubled at the end of the 5-hour period. One particularly important point is the lack of parallelism between the decrease in energy metabolism after nephrectomy and the quantity of urea excreted per hour during the control period. This same statement holds true for the experiments recorded in Table 4.

The results of 2-hour experiments on another series of dogs are given in Table 4. In this case, due probably to the shorter time,

the R–Q does not uniformly show a rise. The decreases in energy metabolism are of the same order of magnitude as those given in Table 2. The blood urea nitrogen has increased approximately 50%.

TABLE 4.—METABOLISM OF NEPHRECTOMIZED DOGS—SERIES II.

Dog. No.	Date.	Wt. of dog, kg.	Average B.M.R per hr.	Basal R-Q.	Wt. kidneys, gm.	Average B.M.R. after nephr.	R-Q after nephr.	Decrease, %.	Decrease per gm., kidney per hr.	Blood urea N before nephr.	Blood urea N after nephr.	Urine urea N per hr., mg.
35	11/5	10.7	18.29	.808	52	15.91	.853	13.0	.045	14.56	17.50	411.6
36	11/6	8.4	14.57	.776	45	12.75	.747	12.5	.040	4.30	7.22	60.2
37	11/7	6.8	13.73	.768	41	12.21	.791	11.1	.037	12.03	13.85	209.9
38	11/8	6.4	14.41	.816	34	11.61	.793	19.0	.081	5.74	7.43	75.7
39	11/11	6.4	13.24	.727	40	11.09	.754	16.2	.054	8.25	11.68	81.3
40	11/12	13.2	19.48	.751	55	17.46	.741	10.3	.037	7.22	14.59	184.6
41	11/13	5.9	10.36	.793	27	8.75	.741	15.5	.060	17.16	22.82	77.6
42	11/19	6.4	13.88	.718	42	12.48	.732	10.1	.033	6.01	7.90	68.6
43	11/20	6.8	12.78	.742	49	11.69	.830	8.5	.022	24.54	29.18	87.5
44	11/21	10.2	18.45	.736	50	15.75	.782	14.6	.054	7.90	13.40	29.8
45	11/22	5.2	9.65	.722	34	8.01	.745	17.0	.048	5.33	8.76	17.7
46	12/10	6.4	12.60	.743	43	10.63	.746	15.6	.046	10.30	14.42	91.8
47	12/11	8.2	17.33	.770	43	14.90	.761	14.0	.057	.....	.....	126.1
48	12/13	8.2	13.83	.711	43	12.26	.807	11.3	.037	7.22	11.33	32.8
49	12/16	7.0	14.28	.754	53	11.91	.777	16.6	.045	6.13	9.14	100.2
50	12/17	6.1	11.41	.733	36	10.14	.734	11.1	.035	5.26	7.94	56.0
51	12/20	8.6	17.79	.712	45	15.47	.755	13.0	.051	7.60	13.61	189.3
52	12/23	6.0	10.31	.730	31	9.53	.755	7.6	.025	7.77	14.28	49.2
53	12/24	5.5	10.30	.745	26	9.92	.804	4.7	.018	13.08	19.74	68.3
54	12/27	7.5	13.56	.721	42	11.58	.707	14.6	.047	9.14	14.46	66.4
55	12/30	6.4	10.11	.777	31	9.18	.759	9.2	.030	9.65	15.30	56.4
Av.				750			.767	12.6	.043	9.50	13.80	

Discussion. Our values for reduction of heat production after nephrectomy are in almost exact agreement with those obtained by Dock[4] for the rat kidney. However, he did not deduct the decrease due to operation alone as we have done and as we believe necessary in gaining an approximate estimate of the proportion of kidney oxygen consumption to the total consumption of the body. Our results also agree with the higher figures of Barcroft and Brodie[1a,b] and are somewhat higher than those of Van Slyke and coworkers.[10] Both of these groups of investigators used the more direct method of measuring blood flow and arteriovenous oxygen difference. The fact that our values fall near the same range seems of some significance. It should be emphasized that all who have worked on this problem have found great variations in the metabolism of the kidney.

The values of 4 to 7% of the total metabolism, obtained by

deducting the decrease due to trauma from the decrease after nephrectomy, are a little lower than those of Tangl.[9a] This may be due to the fact that his animals were curarized instead of anesthetized and the afferent nerves were theoretically functional.

In the 5-hour experiments the R–Q showed a fair rise. This, we believe, indicates gradual elimination of carbon dioxide with the accumulation of non-volatile acids in the blood and tissues. The 2-hour experiments did not show this effect to so great an extent, because the time was so much shorter.

Blood urea nitrogen accumulates at a uniform and constant rate being increased about 50% in 2 hours and 100% in 5 hours. This is in agreement with Bollman, Mann and Magath.[2] Calculation of the amount of accumulated urea from the increase in blood level and referring it to the amount which should have accumulated according to the basal rate of excretion gave a value which would coincide with equal diffusion throughout about 70% of the body tissues. However, the variation between animals was very great, we have no blood-volume figures at the different times, so we have not considered this figure to be of any significance. We have omitted the calculation from our tables due to lack of space.

There is, apparently, no correlation between the urea excretion of the basal period and the decrease in heat production after nephrectomy. This finding appears to be in contrast to that of Gremels[6] but confirms Van Slyke and coworkers.[10]

Conclusions. After bilateral nephrectomy in the dog:

1. Heat production decreases 3 to 7%.
2. Blood urea nitrogen increases approximately 50% in the first 2 hours after nephrectomy and is doubled in about 5 hours.
3. The decrease in heat production bears no relationship to the amount of urea being excreted during the control period before nephrectomy.
4. The R–Q rises after nephrectomy probably due to the accumulation of non-volatile acids in blood and tissues.

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TUBERCULIN SKIN SENSITIVITY IN CHRONIC TUBERCULOSIS IN THE COURSE OF HOSPITAL TREATMENT.

MEASUREMENT BY STANDARD TUBERCULIN (PURIFIED PROTEIN DERIVATIVE).

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IT is known that in chronic tuberculosis variations in the intensity of the tuberculin reaction occur. In a small proportion of cases the original allergy, or heightened capacity of the tissue to react to tuberculin, gives way to anergy, the condition of complete failure of the tissues to respond. Since tuberculin allergy is such a conspicuous feature of tuberculosis, repeated effort has been made to correlate fluctuations in allergy and the appearance of anergy with the clinical course of the disease.

In general, two theories are applied in explanation of depressed allergy or the appearance of anergy. As far back as 1906, Wassermann[12] referred these states to the development of a specific antibody, "antituberculin," which circulated and neutralized freshly introduced tuberculin. With variation in interpretation, and some disagreement on details, a large German school has adopted this explanation of depressed tuberculin allergy as an antibody phenomenon. According to their view "anergy" of a certain type is a manifestation of immunity. The coincident anergy and clinical arrest which may follow prolonged administration of tuberculin have long been cited as the best evidence for the close relationship of the anergic and the immune state.

Such anergy is commonly termed "positive anergy," in contradistinction to "negative anergy" as exemplified in miliary tuberculosis and far advanced tuberculosis with cachexia. In the latter states, in the view of the school just cited, the antibodies of the blood and tissues are more than neutralized by the flood of antigen, specifically tuberculin, entering the circulation in severe, proprogressive tuberculosis.

In this country, on the other hand, there has been a notable tendency in recent years to refer the depressed reactive capacity

following prolonged tuberculin administration, and the anergy of tuberculous pneumonia and miliary tuberculosis, to "desensitization." The chief effort has been not to show that anergy can be explained on the basis of immunity (*i. e.*, the "positive anergy" of the German school), but that immunity can exist in spite of this lack of allergy (see Rich and McCordock,[9] Derick, Branch and Crane[4] and Cummings and Delehant[3]).

Whatever is finally accepted as the underlying explanation for subsidence of allergy in active tuberculosis, it seems important that clinicians be reminded that such subsidence does often occur and that it may be found in tuberculosis both of favorable and unfavorable course.

At the present time there is increasing effort to correlate tuberculin allergy and tuberculous activity. A few of many studies may be cited. Ayman[1] has attempted to find a dosage of tuberculin to which patients with active tuberculosis are positive, and nontuberculous patients negative. A dilution of 1 to 50,000 of the old tuberculin in his possession seemed to be such a dose, but he freely admitted that severely ill tuberculous patients, with high fever and bronchopneumonic areas in the lungs, were prone to be negative to this dose.

Westwater,[13] also attempting a quantitative use of the tuberculin test, had some success in correlating types and severity of tuberculosis with skin sensitivity. Massive disease and exudative lesions were found to be associated with low sensitivity, and slight lesions and fibroid tuberculosis with the reverse. The more recent and active the disease the higher the sensitivity. Among patients getting worse on routine treatment, sensitivity remained stationary or diminished, whereas it commonly increased with clinical improvement. Acute excavation was found to be associated with high allergy, whereas a low degree of allergy was found with old cavities. Collapse therapy appeared to reduce sensitivity to tuberculin, and this fact was explained on the ground of desensitization following lymph stasis in the lung.

Neal[7] noted that a considerable number of patients under pneumothorax treatment, as they improved, became negative to tuberculin, and was led to the conclusion that the tuberculin test might be used as a guide for the termination of pneumothorax treatment. Paretsky,[8] in following over a thousand cases of positive reactors, saw 80 become negative to tuberculin. Their sensitiveness had decreased from the point where they were sensitive to the customary diagnostic doses of old tuberculin, to the point where they failed to respond to the excessive dose of 10 mg. In every case where loss of tuberculin allergy occurred in what was originally active disease, the disease had become arrested.

Other studies might be cited, but these illustrate the general trend. Most investigations have dealt with the complete disappear-

ance of the tuberculin reaction. A few have been concerned with fluctuations in the intensity of tuberculin sensitiveness. A great difficulty has been in the choice of a suitable method for studying the latter. Variable factors have been the dosage of the tuberculin and the quality of different tuberculin preparations.

The simplest method is to measure the varying size of reaction to a given dose. However, in general the method of serial dilution and determination of the threshold at which reaction occurs, has been found sharper in its results (Schwartz and Heise,[10] Johnston, Howard and Maroney).[5] The latter method, on the other hand, suffers from cumbersomeness and difficulty in application where a large number of patients are under observation.

Methods of Investigation. The object of the present investigation was to study fluctuations in the level of tuberculin hypersensitiveness in chronic tuberculosis, and correlate them if possible with changes in the clinical course. Since a general impression seems to exist among clinicians that pleural effusion in tuberculosis is followed by reduction in sensitiveness to tuberculin, effort was directed particularly toward the investigation of this problem. Since pleural effusion is a common complication of artificial pneumothorax, it was thought that frequent tuberculin tests in patients under pneumothorax treatment would, in a certain number of cases, through ordinary chance just precede the appearance of a pleural effusion, permitting subsequent study of the fluctuation, if any, in the intensity of the tuberculin reaction.

This investigation differs from previous ones in that standardized tuberculin, *viz.*, the Purified Protein Derivative (PPD),[11] was employed throughout. The use of a product of constant strength is obviously necessary in such a study, since small differences in reaction, due to variation in the tuberculin used, might be attributed to fluctuations in the level of the patient's sensitiveness. Another obvious source of error in such a study is individual variance in measuring the size of reactions. The present investigation is subject to criticism on that score, because the actual tests were carried out by a series of workers, each conducting the tests for 3 to 4 months. Actually, however, uniformity in reading and measuring reactions was ensured by uniform training and practice in the Institute, and overlapping periods of several weeks in the hospital as one investigator took the problem over from another. Even with this precaution, in tabulating results, variations in sensitiveness were not looked upon as significant unless they departed by more than 50% from the size of the reaction at the beginning of the study.

The investigation was made on 116 ward patients in the tuberculosis services of Drs. Frank A. Craig and H. W. Hetherington in the Philadelphia General Hospital. Two-thirds (66%) of the group, were classified as far advanced when the study was begun; 24% as moderately advanced and 10% as minimal or suspected tuberculosis.

The plan at the outset was to test a large group once a month with the hope that a considerable number of patients, sufficient for drawing conclusions, would remain under observation for the course of the experiment, which was arbitrarily set at 1 year. However, numerous deaths occurred, and discharges from the hospital, with or against advice, were so many that only 67 remained long enough for what was considered minimal required observation of the trend of tuberculin sensitiveness. This minimum was set at 4 months, permitting 5 monthly tuberculin tests. Of the entire group, 20 received 10 or more monthly tuberculin tests.

Of the 67 patients remaining long enough for satisfactory observation, 34 were under pneumothorax treatment. In most of them the procedure was initiated in the hospital. Since, as already noted, pneumothorax is often complicated at some period in its course by tuberculous pleuritis with effusion, it was believed that considerable opportunity would occur for study of the effect of pleural effusion on the tuberculin reaction. Actually 21 of the 34 patients under pneumothorax treatment developed effusions in the course of treatment. In addition, 3 cases of pleural effusion occurred among the 33 patients not under pneumothorax treatment. A little less than half of the effusions occurred so early in treatment, or at such a long time interval from the next tuberculin test, that their relation to skin sensitiveness seems quite uncertain. In 13 cases, or more than half, however, the time relations of effusion and test were such that it seemed fair to draw conclusions.

It is evident from the previous studies cited that variations in skin sensitivity can best be detected by small doses of tuberculin. As pointed out, patients with progressive or advanced tuberculosis are not highly sensitive to tuberculin, and are in fact much less sensitive than healthy persons in contact with open tuberculosis. Originally it was planned to give all patients in the study 3 tests with the Purified Protein Derivative tuberculin, *viz.*, the standard first dose, the second dose (used in routine testing for those failing to react to the first dose), and a very small dose, one-tenth the size of the small standard first dose, calculated to discover the lower limits of sensitiveness. Actually it proved impossible to gain general consent for the three injections, and in the study, as it was carried to completion, the gross standard second dose was omitted, and only two injections were given each month, *viz.*, the standard first dose of the Purified Protein Derivative (0.00002 mg.), and one-tenth of this amount (0.000002 mg.). This proved a fortunate selection; for in these dilutions the Purified Protein Derivative afforded a delicate indicator of the degree of tuberculin sensitiveness. The lower strength commonly appeared to be the threshold value.

Tuberculin Sensitivity of the Patients Studied. The general level of sensitivity to tuberculin was low. In the entire group of 116 patients there were no strong reactions to 0.00002 mg. of the Purified Protein Derivative. Indeed in the whole group only 2 patients gave reactions consistently averaging more than a two plus reading, *i. e.*, reactions in which the dimensions of the inflammatory swelling exceeded 20 by 20 mm. These patients were among the 47 tested for periods of 4 to 10 months. One was a colored male remaining 9 months and the other a white female tested for 8 months. Of the 20 remaining for 10 months or more not a single one averaged more than a two plus reaction to the stronger of the 2 cases.

Of the 116 patients 8 were negative to the stronger of the chosen doses of the Purified Protein Derivative throughout the whole course of their study. These were not tested with the standard second dose of Purified Protein Derivative (which is 250 times the size of the standard first dose), so that it is impossible to say whether they were tuberculin-negative or not. Experience in other patients has shown that most tuberculous patients negative to the first of the standard doses do respond to the second.[6]

The suitability of the two chosen doses as indicators of the lower limits of tuberculin sensitiveness in the patients of the series is

shown by comparison of the results of testing with the standard first dose of the Purified Protein Derivative and a dose one-tenth this size. Twenty-seven per cent (31 of 116) of the entire group were negative to the first dose (0.00002 mg.) two-thirds of the time, while 72% (83 in 116) were negative to one-tenth of the standard first dose (*i. e.*, to 0.000002 mg.) through two-thirds of the period of testing.

Fluctuation in Sensitiveness to Tuberculin. The 2 cases charted in Table 1 demonstrate the threshold of tuberculin sensitiveness,

TABLE 1.—THRESHOLD AND FLUCTUATION OF SENSITIVENESS TO TUBERCULIN.

Date, 1935.	Patient, A. P., colored male, aged 15, far advanced tuberculosis, sputum positive for tubercle bacilli. Size of reaction in millimeters		Patient, M. D., white female, aged 40, moderately advanced tuberculosis, sputum recorded as negative, pleural fluid positive for tubercle bacilli. Size of reaction in millimeters.	
	0.00002 mg. PPD.	0.000002 mg. PPD.	0.00002 mg. PPD.	0.000002 mg. PPD.
May 2	15 x 16 x 1	12 x 11 x 1		
June 14	Omitted	12 x 11 x 1		
July 17	25 x 20 x 2	12 x 10 x 1		
Aug. 15	16 x 14 x 2	11 x 10 x 1	12 x 11 x 1	Neg.
Sept. 4	15 x 13 x 3	12 x 11 x 2	14 x 10 x 2	Neg.
Oct. 6	12 x 11 x 2	Neg.	10 x 5 x 1	7 x 5 x 1
Nov. 7	Trace	Trace	Trace	Trace
Dec. 4	10 x 8 x 1	Trace	8 x 6 x 1	Neg.
1936				
Jan. 7	15 x 14 x 1	10 x 8 x 1	18 x 14 x 1	Neg.
Feb. 5	22 x 20 x 2	14 x 12 x 1	8 x 7 x 1	Neg.
Mar. 10	20 x 20 x 2	13 x 12 x 1	14 x 10 x 1	10 x 8 x 1
Apr. 21	30 x 25 x 2	14 x 12 x 1	10 x 8 x 1	Neg.
	Patient improving		Patient improving	

and may be cited also as examples in the study of fluctuation in sensitivity. The first, A. P., shows a type of curve seen a number of times, in which the intensity of response to tuberculin started at a fairly high level, dropped considerably and finally returned to the original level. In this case, under the standard set, the variation in size of reaction is considered significant. In the other case, M. D., we considered the range in size of reaction for the most part within the limits of experimental error. The threshold is apparent. We have recorded this case as one in which no significant persistent change in the level of sensitiveness occurred. In the October-December period, however, an unmistakable depression of tuberculin sensitivity occurred. It is noteworthy that this was coincident with an acute pulmonary consolidation. This cleared subsequently and in succeeding months this patient improved.

Of the 67 patients studied over a period of 4 months or more, 39, or more than half, maintained approximately the same level of sensitiveness throughout the period of observation. In several of these cases, however, the level was a negative reaction. Twelve of the 20 who were under observation for 10 months to a year maintained the same level of sensitiveness. All of the others fluctuated in the degree of their response to tuberculin.

In the beginning of the experiment it was thought that a seasonal variation in sensitiveness might be found. Actually the largest reactions occurred in many of the patients in the summer of 1935, followed by a lower level in the succeeding months. This might be attributed to seasonal influence, but it is to be noted that the study began in the early summer and that in a large percentage of the patients the clinical course was down hill from the beginning. It is quite possible that the high summer level was merely a reflection of the better clinical condition at the beginning of the study. Schwartz and Heise,[10] it may be noted, were unable to correlate fluctuations with seasonal change.

TABLE 2.—SENSITIVENESS TO TUBERCULIN IN PATIENTS GETTING BETTER AND WORSE.

	Patient, A. D., white female, aged 25, far advanced tuberculosis, sputum positive for tubercle bacilli.		Patient, M. K., white female, aged 27, far advanced tuberculosis.	
	Size of reaction in millimeters.		Size of reaction in millimeters.	
Date, 1935.	0.00002 mg. PPD.	0.000002 mg. PPD.	0.00002 mg. PPD.	0.000002 mg. PPD.
May 2	Listed plus	10 x 9 x 1		
June 14	Omitted	Trace	Omitted	Neg.
July 17	15 x 16 x 3	Neg.	11 x 10 x 1	5 x 5 x 1
Aug. 15	15 x 10 x 1	Neg.	14 x 9 x 1	Neg.
Sept. 4	25 x 20 x 2	14 x 12 x 1	8 x 6 x 1	7 x 7 x 1
Oct. 6	10 x 8 x 1	Trace	18 x 18 x 1	Trace
Nov. 7	Neg.	Neg.	Trace	Neg.
Dec. 4	10 x 10 x 1	Neg.	Trace	Neg.
1936				
Jan. 7	Neg.	Neg.	Neg.	Neg.
Feb. 5	12 x 10 x 1	Trace	Trace	Neg.
Mar. 10	Trace	Neg.	6 x 5 x 1	Neg.
Apr. 21	Neg.	Neg.	Trace	Neg.
	Patient improving		Patient becoming progressively worse	

A continuous drop in sensitiveness occurred as a rule in patients whose disease was becoming steadily worse (*e. g.*, patient M. K., Table 2). Very often the reaction was negative to the doses used for 3 or more months before death. On the other hand, in a still larger number of patients who showed signs of clinical improvement, with loss of fever, slight gain in weight and slight clearing of Roentgen ray evidence of infiltration, a continuous drop in sensitiveness occurred. Patient A. D., Table 2, is an example. This experience may be compared with that reported by Paretsky.[8] The patients of our series were not shown to be tuberculin negative, as strong doses of tuberculin were not used. Nor did they become arrested, as was the case with Paretsky's patients who became negative. Ours were too far advanced, for the most part, to hope for arrest, but their dropping sensitiveness with improvement might be analogous to the loss of sensitiveness, reported by Paretsky with complete arrest of the disease.

No correlation could be established between patients' temperature and their sensitivity to tuberculin. The majority of patients in the

series were not febrile. A few had temperatures rising as high as 103°. The clinical course in these patients was bad, and in general they did not react to the two doses of tuberculin used. However, several patients who were afebrile and improving also were insensitive to the doses of tuberculin used. Cases were seen in which an increasing sensitiveness to tuberculin coincided with a rise in afternoon temperature, and the reverse was also seen.

The course of tuberculin sensitivity in the 67 patients observed through five or more monthly injections is summarized in Tables 3 and 4.

TABLE 3.—TWENTY TUBERCULOUS PATIENTS RECEIVING MONTHLY TESTS WITH TUBERCULIN FOR 10 OR MORE MONTHS.

Far Advanced Cases (14 *Cases*)

(Average age 25 yrs., age range 12 to 41 yrs.)

7 maintained an approximately level skin sensitiveness with minor fluctuations; 2 of these were consistently negative to the doses of tuberculin used. Three improved clinically, 1 grew worse and 3 showed no change.

7 decreased steadily in skin sensitiveness. Four of these improved clinically, 2 grew worse, and 1 showed no change.

Moderately Advanced Cases (6 *Cases*).

(Average age 25 yrs., age range 13 to 31 yrs.)

5 maintained an approximately level skin sensitiveness, with minor fluctuations. Two of these improved clinically, 1 grew worse and 2 showed no change.

1 decreased steadily in skin sensitiveness. No clinical change occurred in this case.

TABLE 4.—FORTY-SEVEN TUBERCULOUS PATIENTS RECEIVING MONTHLY TESTS WITH TUBERCULIN FOR 4 TO 10 MONTHS.

Far Advanced Cases (30 *Cases*).

8 increased in skin sensitiveness. Five of these improved clinically, 2 grew worse, but with periods of transient improvement, and 1 showed no change.

18 maintained an approximately level skin sensitiveness with minor fluctuations; 5 of these were consistently negative to the doses of tuberculin used.

4 steadily decreased in skin sensitiveness. Three of these grew worse and one showed no change.

Moderately Advanced Cases (11 *Cases*).

3 increased in skin sensitiveness. Two of these improved clinically, and 1 showed no change.

5 maintained an approximately level skin sensitiveness, with minor fluctuations.

3 steadily decreased in skin sensitiveness. Two of these improved clinically and 1 grew worse.

Minimal or Suspected Cases (6 *Cases*).

2 increased in skin sensitiveness.

4 maintained an approximately level skin sensitiveness, with minor fluctuations.

A contrast will be noted between Tables 3 and 4 in that 13 or 28% of the patients remaining the short period exhibited a rise in skin sensitiveness as compared with none among the patients remaining the longer period. The explanation lies in part in the composition of the two groups. Those remaining the shorter time were as a group in somewhat better clinical condition, even though the disease was anatomically advanced, and difficult to hold in the hospital.

The rise in sensitiveness of so many of them may reflect some slight improvement in their clinical state.

Fluctuation in Sensitiveness as a Result of Collapse Therapy and Pleural Effusion. In the patients of this series pneumothorax *per se* appeared to have little if any influence on skin sensitivity to tuberculin. *A priori*, explanations could be formulated for either a fall or a rise in general tuberculin skin sensitiveness, for the former on the ground of desensitization by increased absorption of tuberculous matter retained in the non-moving lung, and for the latter on the ground of expulsion of infective material from the collapsed lung, and consequent relief from an already existing desensitizing process. Actually pneumothorax was initiated so gradually that neither of these effects could well be expected. In a number of cases the intensity of the reaction decreased in the months following the induction of pneumothorax, but to no greater degree than in an equal number of patients, without pneumothorax, following a similar clinical course.

This experience, it may be noted in passing, might be compared with that recently reported by Neal,[7] but no patient in this series improved within the time limit of the study to the extent of arrest, as in Neal's patients who became negative to tuberculin after several months to several years of treatment.

Loss of sensitivity, from sudden excessive absorption of self-manufactured tuberculin and corresponding desensitization might be expected to follow thoracoplasty. "Tuberculin shock" after thoracoplasty has been described (Coryllos).[2] In our series decrease in the intensity of the tuberculin reaction followed thoracoplasty in 3 out of 4 cases where this operation was performed. In 1 of these cases each of two stages was followed by a slight drop in the intensity of the reaction. The number of cases is obviously too small to permit generalizations.

TABLE 5.—TWENTY-FOUR TUBERCULOUS PATIENTS WITH PLEURAL EFFUSIONS RECEIVING MONTHLY TESTS WITH TUBERCULIN FOR 5 TO 12 MONTHS.

Sequel of Appearance of Fluid.

1 increased in skin sensitiveness.

4 showed no change in skin sensitiveness; in 3 of these the reaction to tuberculin was almost negative both before and after the appearance of the effusion.

8 definitely decreased in sensitiveness.

11 showed no change from which conclusions could be drawn; in these cases fluid was present at the beginning of the study or appeared so long before the next tuberculin test that any immediate effect was considered undiscovered.

The study did, however, afford results on the effect of pleural effusions, which merit some consideration. Table 5 summarizes the course of response to tuberculin in the 24 cases of effusion. As noted, 21 of these were in patients with artificial pneumothorax. Of the 20 patients under observation for approximately 1 year 13 had pleural effusions; in 12 of the 13 the effusion was a complication

of pneumothorax. As the table shows, in the majority of cases permitting conclusions, the advent of tuberculous pleural effusion was followed by a decrease in the intensity of the tuberculin reaction. It is noteworthy that in 1 case the removal of fluid by aspiration was followed by an abrupt change from a negative to a positive reaction.

Thus if any conclusion can be drawn from the series of tuberculin tests in patients whose pulmonary tuberculosis was complicated by effusion, it is that the latter depresses tuberculin sensitivity. Such an effect might be explained on the ground of desensitization from absorption of exudate rich in tuberculo-protein. It should be recalled that pleural effusions are often rich in tubercle bacilli, for the most part enmeshed in the fibrin layer adhering to the pleural surfaces. In the early days of the effusion before appreciable fibrous organization of this fibrin occurs, considerable absorption of autolytic products might take place through the highly vascular pleural membranes. Possibly further collapse of the lung by the exudate might play some rôle.

It must not be forgotten, however, that among the patients suffering pleural effusions were many whose general course was unfavorable, and that among such patients in general many exhibited decreasing sensitivity. It is thus entirely possible that instead of the depression in sensitiveness being related to the effusion, both are to be attributed to progression of the pulmonary disease.

Summary. Fluctuations in the intensity of the tuberculin skin reaction were studied by monthly tests in 116 ward patients with chronic pulmonary tuberculosis. Twenty patients remained under observation approximately 1 year and 67 for more than 4 months. To ensure uniformity, standardized tuberculin (Purified Protein Derivative) was used throughout the experiment. Two doses, *viz.*, 0.00002 mg. (the standard first dose) and 0.000002 mg. (one-tenth of the standard first dose) were employed on each patient. In most cases one or the other of these detected the threshold of reaction.

The general level of sensitiveness to tuberculin was low. Strong reactions were never seen. Of the 20 patients remaining under observation approximately a year not one averaged more than a 2+ reactions to the stronger of the 2 doses. Eight of the 116 patients were negative to both doses for the whole course of their study. To the stronger dose 27% of the entire group were negative, and 72% to the weaker dose, two-thirds of the time.

Of the 67 patients injected at 5 or more monthly intervals, more than half maintained approximately the same level of sensitiveness, as did 12 out of 20 followed for approximately a year. The fluctuations in the remainder were of inconstant character, but certain consistent trends were observed. While, as is already well known, patients with unfavorable course tended to lose their tuberculin sensitiveness as the end approached, a definite continuing depression

of sensitivity was observed also in patients with chronic tuberculosis of long duration, but somewhat favorable course. On the other hand, transient or prolonged increase in sensitiveness occurred in numerous patients with clinical improvement.

Observation was directed particularly toward the effect of special therapeutic procedures employed, and also toward such events as pulmonary spread of the disease, and particularly pleural effusion. Pneumothorax *per se* had no noticeable effect. In the small number of cases of thoracoplasty observed, a drop in sensitivity followed the operation. In the majority of cases pleural effusion appeared to depress skin reactivity.

No correlation could be established between tuberculin skin sensitivity and the patient's temperature or with seasonal influences.

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CONSIDERATIONS AND EXPERIMENTS ON THE HYPERSENSITIVE NATURE OF AMIDOPYRINE AGRANULOCYTOSIS.

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It appears to be definitely proved that the use of amidopyrine alone or combined with various other drugs in some persons causes agranulocytosis (agranulocytic angina, neutropenia maligna or granulo(cyto)penia maligna).

Persons recovered from amidopyrine granulocytopenia react when given a single dose of amidopyrine with several symptoms, the most constant and important of which is a violent fall of the granulocyte count (Madison and Squier[7]; Zinberg, Katzenstein and Wice[11]; Plum[8a]; Buus-Hansen and Holten,[2] etc.). This granulocyte fall cannot be produced by other drugs, and the reaction cannot be produced by amidopyrine in cases recovered from granulocytopenia maligna caused by other agents, *e. g.*, salvarsan (v. Bonsdorff[1]). These facts seem to me to be of special value as proofs of the etiologic significance of amidopyrine in granulocytopenia maligna.

The question how and why this very serious effect of amidopyrine is produced in the human organism still remains to be solved. In the

following, I shall endeavor to give a brief outline of our present knowledge, describe a few experiments concerning the question and put forward a hypothesis which I hope may be of value.

It is a fact that a very large number of patients and healthy persons have taken amidopyrine, a great many of these in rather large doses and for a long time without any harm whatever. On the other hand, it must be taken for granted that in quite a number of cases—even if it is only a few as compared with the number having taken amidopyrine—this medication has caused granulopenia. These facts appear to show that there cannot be question of a toxic action of amidopyrine in the same sense as for instance in strychnine causing an acute poisoning or a chronic intoxication or salts of heavy metals causing an intoxication acute or chronic. It seems to be certain that amidopyrine granulopenia arises only in persons hypersensitive to this substance. Hypersensitivity to drugs is often called idiosyncrasy, by which term *sensu strictiori* is meant an abnormal state which is displayed by an increased and altered reactivity to the intake of various drugs. This reactivity is characterized by the appearance of certain morbid phenomena, the idiosyncratic symptoms, which are quite independent of the nature and physiologic action of the substance causing the symptoms. The idiosyncrasy depends on an individual disposition and an exposition, a sensitization of an individual naturally disposed. This sensitization is brought about by a *repeated* dosage of substances liable to cause idiosyncrasy. At first the intake of the drug is not followed by any morbid symptoms, but after a varying number of doses the idiosyncratic phenomena appear. These are rather polymorphic, and in different persons the same agent may cause different symptoms, for example acetosalicylic acid may cause exanthems in one person, asthma in another and edema in a third individual.

The liability to provoke idiosyncratic reactions varies for different substances. It seems to be rather small for phenacetin, greater for the barbiturates, for instance, and Nirvanol (Phenylethylhydantoin) provoke idiosyncratic reactions in about 65% of human beings. Amidopyrine is known to produce idiosyncratic reactions fairly often.

The question arises if granulopenia maligna can be recognized as an idiosyncratic symptom as exanthems, asthma, and so forth. This question cannot be answered definitely but I want to point out that a case of granulopenia maligna caused by the drug Nirvanol just mentioned has been reported by Feer.[3] It may be justified to regard the granulopenia in this case as an idiosyncratic symptom as Nirvanol is known to cause such symptoms very often.

It may be mentioned in this connection that leukopenia is a rather common feature in anaphylactic reactions which have much in common with the idiosyncratic reactions. In my opinion, this

tends to show that granulopenia may be regarded as an idiosyncratic phenomenon, and so far there should be no objection against regarding the granulopenia maligna caused by amidopyrine as the result of a sensitization of a naturally disposed individual by the repeated dosage of this drug.

The cases of amidopyrine granulopenia recorded in the literature have arisen after doses extending from a single tablet (in a patient who long ago had got amidopyrine (Zinberg, Katzenstein and Wice[11])) to the continued use of the substance for several months (*e. g.*, a case reported by Buus-Hansen and me[2]). These facts are well in accordance with the concept of granulopenia maligna as an idiosyncratic phenomenon. The time and dosage required to produce idiosyncratic symptoms varies extremely in different individuals. It is well known that a patient may use luminal, for instance, for a long time and then suddenly get skin eruptions; on the other hand, another patient may have an exanthem after only a few doses.

It has also been seen that the granulopenia with accompanying symptoms has not been recognized until 5 days after the last intake of amidopyrine (Case 5, Holten, Nielsen, Transbøl[5]). This together with the other facts just referred to reminds one very much of the facts relating to cinchophen and hepatitis caused by this drug. Exactly as is the case with amidopyrine, very large numbers of persons have taken cinchophen without any harm even for long periods, but a few have had more or less severe liver damage. The parallel between amidopyrine-granulopenia and cinchophen-hepatitis is in a way stressed by the fact that the danger adhering to the use of the drug was not recognized till several years after the introduction of the substance into therapy. Cinchophen was introduced in 1908 and the cinchophen hepatitis was described in 1923. Amidopyrine was produced in 1893. In Scandinavia, it was used very little until cibalgin (a combination with dial *i. e.*, diallylo-barbituric acid) was introduced in 1925. In 1934, amidopyrine agranulocytosis was recognized in Scandinavia. Like amidopyrine cinchophen produces idiosyncratic reactions fairly often. Quick[9] thinks it logical to assume that the hepatitis is also an idiosyncratic phenomenon when caused by cinchophen. He calls attention to the Arthus phenomenon, the subcutaneous necrosis produced by subcutaneous injections of heterologous protein after sensitization of animals with this protein. Necrosis or sterile inflammations as idiosyncratic reactions may arise in other places than the skin, viz., in the lungs, kidneys, joints, brain and liver. Quick regards the hepatitis, a sterile inflammation or a necrosis, in cinchophen poisoning as an Arthus phenomenon. One may transfer Quick's hypothesis for cinchophen-hepatitis to granulopenia maligna. The essential pathologic condition here is in the bone marrow where the neutrophils and their mother cells are almost or entirely lacking. This may

be due to a partial necrosis or something near to it of this part of the bone marrow. The erythropoiesis and thrombocytogenesis is not affected, and it is in good accordance with modern views on bone-marrow function to regard the 3 main functions of the marrow as bound to separate systems.* I believe it to be a fertile working hypothesis to regard the bone-marrow reaction in amidopyrine granulopenia as an Arthus phenomenon localized to the leukopoietic part of the bone marrow. Experimental work along this line is in progress.

Turning now to the experimental work done to elucidate the pathogenesis of amidopyrine granulopenia, I refer again to the experiments in patients recovered from an attack of this disease. A single dose of amidopyrine causes as already mentioned a rapid fall of the leukocyte count lasting for several days. In a few cases (*e. g.*, one of Plum's[8b] cases) this fall did not occur until a couple of days after the intake of the drug, whereas in the majority of the experiments it comes after ½ to 1 hour. The retardation of the reaction has its parallel in serum sickness, where some symptoms do not arise until after several days after the serum injection.

It is well worth adding that Plum[8b] has shown that the amount of polynuclear cells in the bone marrow, as shown by sternal puncture, decreases rapidly and for a long time in experiments of this kind. This very clearly shows that the changes produced take place in the bone marrow and are not limited to the peripheral blood.

The view has been advanced that the granulopenia maligna from amidopyrine was due to some unknown impurity of the drug and in support of this view it has been stated that all cases of amidopyrine granulopenia reported were produced not by the original Pyramidon Bayer but by substitutes. This view, however, will not hold as Kloster[6] has reported a case after Pyramidon Bayer which recovered and was tested with Bayer's preparation and showed the typical severe leukocyte drop.

The attempt to produce granulopenia in animal experiments has not had great success. Madison and Squier[7] had one rabbit out of 18 which got granulopenia, and Hoffman, Hickey and Butt[4] reported some experiments (without stating definite dates), where the experimental animals had large falls of leukocyte counts after very large doses of amidopyrine. My coworkers Nielsen and Transbøl and I[5] have given amidopyrine to 26 rabbits and 2 guinea pigs. The doses varied from 2.5 to 250 mg. per day, and the animals were treated for 30 to 90 days, in several cases intermittent dosage was tried. Leukocyte counts including differential counts were made with intervals from 1 day to 1 week. In no case could definite leukopenia be seen. The leukocyte count varies—from 4500 to 16,000. The granulocyte count varies from 30% to about 80%.

* For histologic descriptions of the bone marrow in granulopenia maligna, see Holten, Nielsen and Transbøl, loc. cit.

Of course, one must be very cautious in concluding that amidopyrine dosage has produced leukopenia. As an example showing this very clearly I quote an experiment:

Guinea pig.

Feb. 7. Leukocytes, 11,900. Neutrophils, 81%.
2.5 mg. amidopyrine by mouth from Feb. 7 until March 11. Leukocytes counted 6 times: 7450 to 14,800. Neutrophils, 30 to 70%.
March 12, 13 and 14, no amidopyrine was given.
March 15, 10 mg.; on March 16, 17 and 18, nothing was given.
March 17: Leukocytes, 4500 with 54% neutrophils.
March 18: Leukocytes, 12,500 with 58% neutrophils.
March 19: Leukocytes, 16,000 with 44% neutrophils; 10 mg. amidopyrine.
March 20: Leukocytes, 13,100 with 66% neutrophils.
March 21: Leukocytes, 12,700 with 47% neutrophils.
March 22: Leukocytes, 14,300 with 30% neutrophils; 20 mg. amidopyrine.
March 23: Leukocytes, 10,600 with 45% neutrophils; 20 mg. amidopyrine.
March 24: Leukocytes, 12,500 with 58% neutrophils; 20 mg. amidopyrine.
March 28: Leukocytes, 15,500 with 71% neutrophils; 20 mg. amidopyrine.

On March 17 we thought we had produced leukopenia, but the subsequent course did not confirm this belief. The drop was probably only a spontaneous variation.

On the whole, I believe one must say that animal experiments have hitherto given no certain evidence and have not contributed to the solution of the problems. However, if it is assumed that the granulopenia is an idiosyncratic reaction one cannot wonder at this. Such reactions cannot be produced with the same frequency and under similar forms in different species, and man seems to be more predisposed than any other.

Experiments have been briefly published tending to show that bone-marrow changes could be found in animals given amidopyrine without any demonstrable changes in the peripheral blood. Until details are published, I believe it wise to consider this with some reservation.

We have made some experiments to prove the idiosyncratic nature of amidopyrine granulopenia in man by trying to transfer the idiocyncrasy passively. Serum from a case of amidopyrine granulopenia drawn under sterile precautions was injected intracutaneously in 2 healthy individuals. No hyperemia or any other sign of hypersensivity appeared after 24 hours. The injection of amidopyrine solution (and a couple of other substances for control) at the points of serum injection produced no local or universal symptoms whatever. This means that the "reagins" are not to be found in the circulating blood or that the substance producing idiosyncrasy is not amidopyrine but amidopyrine which has undergone some alteration or other in the human organism.

In a patient in whom hypersensivity to amidopyrine had previously been proved,[2] serum from a healthy person who 1 hour before had taken 300 mg. amidopyrine was injected intracutaneously; as a control serum drawn previous to the intake was also injected. No

local or universal reaction whatever occurred. Hence we did not succeed in showing skin hypersensitivity to serum containing amidopyrine in a person proved to be hypersensitive to amidopyrine when taken by mouth.

Squier and Madison[10] have been able to demonstrate cutaneous hypersensitivity in convalescents from amidopyrine granulopenia by placing patches of linen with a suspension of amidopyrine on the skin. Buus-Hansen and I[2] have not been able to confirm this in our hypersensitive patient, but the patient had a slight but certain drop of her leukocyte count.

Summary. 1. It can be stated as definitely proved that amidopyrine can cause granulopenia maligna.

2. The mechanism of this is not known but it is not similar to the common toxic action of drugs. An individual hypersensitivity appears to be necessary; this hypersensitivity may be produced after a very short or a very long use of amidopyrine.

3. Parallels between amidopyrine-granulopenia and cinchophen-hepatitis are drawn. It is suggested that granulopenia may be caused by a kind of Arthus phenomenon in the bone marrow.

4. The author and his coworkers have failed to produce granulopenia in animal experiments.

5. We have likewise not been able to transfer "amidopyrine allergy" passively.

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THE GENERAL HOSPITAL; ITS PSYCHIATRIC NEEDS AND THE OPPORTUNITIES IT OFFERS FOR PSYCHIATRIC TEACHING.

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It has been variously reported that personality disorders (*i. e.*, psychiatric problems) constitute anywhere from 35 to 75% of the case load of the general practitioner. Insofar as the author has been able to learn, these figures, though probably they are fairly

* A part of the Department of Psychiatry, Colorado University School of Medicine, financed by the Rockefeller Foundation.

accurate, are estimates not based on any statistical studies. Certainly the significant importance of the frequency in occurrence of such disorders, in general hospital and general medical practice, is rapidly coming to the fore as indicated by the ever increasing number of publications dealing with the topic.

One of the objectives of our Psychiatric Liaison Department,* organized September, 1934, has been to determine the frequency with which psychiatric problems occur in the average general hospital and dispensary patient population, to develop workable procedures for studying and treating these problems, and to evaluate, in general, the opportunities offered by the general hospital and dispensary for acquainting the medical student and intern with the diagnosis and treatment and possible prevention of such reactions

Scope of Report. This report deals simply with statistical studies concerning the frequency of occurrence of such disorders in a general hospital and dispensary patient clientéle; and, with the opportunities offered by such a clinical organization as the general hospital for preparing the medical student and intern for the adequate and economical management of such patient problems as will come to them in the general practice of medicine. Our statistics are based on the patients admitted to the Colorado General Hospital Dispensary between September 14, 1934, and September 1, 1935 (*i. e.*, 11½ months), and on the admissions to the wards of the Colorado General Hospital between September 15, 1934, and March 30, 1936 (*i. e.*, 17½ months).

Basis of Statistics. This analysis is made on the statistics as recorded by the "record" † organization of the hospital and on those kept by the Psychiatric Liaison Department. Any patient seen for the first time in any of the 18 clinics of the outpatient dispensary was regarded as a "new" case. Thereafter, such a case visiting the clinic was regarded as an "old" one. In the outpatient department the psychiatrist only examined patients referred by these clinics. A patient seen only once in some other department before being referred for psychiatric study was considered "new." The only exception was made in the instance of the medical clinic referrals. In that clinic, because there were but few physicians to handle the very large case load, on an average of 5 visits were required of the patient before all of the complete studies desired by that unit for diagnosis could be made. Therefore, a "new" case referred to the psychiatrist from the medical clinic connotated a case seen in that clinic not more than five times and referred as soon as the medical examination was finished. Any other patients referred to the psychiatrist were considered "old" cases.

All patients admitted to the wards of the hospital were either "new" cases or those temporarily "away on leave." The latter were not considered new admissions when returning for further hospitalization. Thus the delineations made in regard to new and old cases, in the instance of the dispensary patients, were not necessary when considering those coming to the hospital proper.

Incidence of Psychiatric Problems in the Outpatient Department. During the 11½ months' period, 9792 "new" cases came to the dis-

* Billings, E. G.: J. Am. Med. Assn., **107**, 635, 1936.

† The author wishes to thank Miss Margaret Neale, Director of the Record Room, and Mrs. Della Smith, formerly supervisor of the Outpatient Department of the Colorado General Hospital, for their assistance in compiling the statistics.

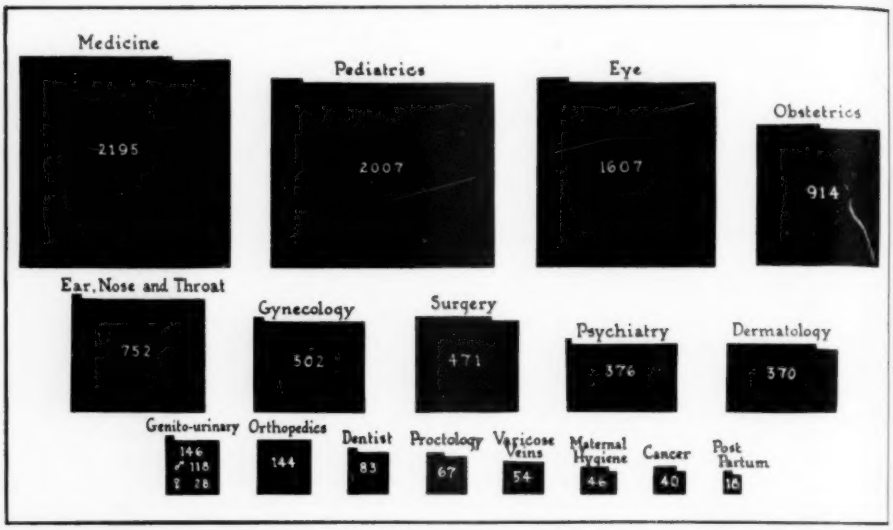

FIG. 1.—Relative teaching importance of dispensary clinics in Colorado General Hospital based on number of new cases admitted to each during year 1934–1935.

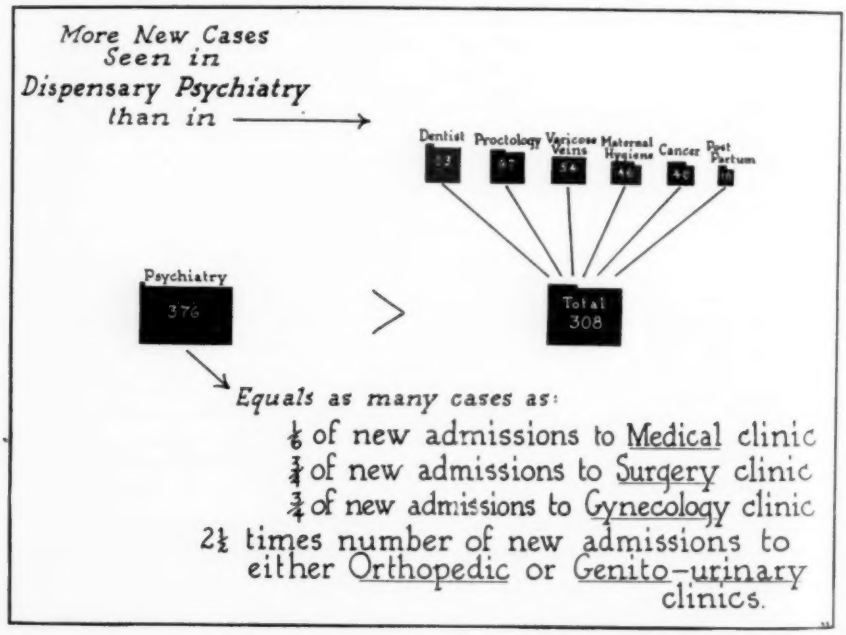

FIG. 2

pensary. Of these, 376 patients (3.83%, or 1 out of every 28 admissions) were referred for psychiatric study after their initial examination. (There were also referred 299 "old" cases which are mentioned here only because the total of "old" and "new" cases examined psychiatrically is utilized in an analysis of the referring source to be discussed later.) When the "new" cases admitted to each of the 18 clinics of the dispensary and the "new" cases referred to the psychiatrist are separately and graphically plotted (Fig. 1), the block of psychiatric material as found in the dispensary stands eighth in the series. As relatively viewed in another way, there were more "new" cases seen by the liaison psychiatrist, in the outpatient department, than were seen in dentistry, proctology, varicose-vein clinic and post-partum clinic combined (Fig. 2). These psychiatric cases in number approximately equaled: $\frac{1}{6}$ of the new admissions to the medical clinic; $\frac{3}{4}$ to the surgical clinic; $\frac{3}{4}$ to the gynecology clinic, and $2\frac{1}{2}$ times the number admitted to either the orthopedic or genitourinary clinics.

There were in all ("old" and "new") 675 cases referred to the psychiatrist by 12 of the 18 departments. The majority (70.2%) were so relegated by the medical clinic (Table 1).

TABLE 1.—SOURCE OF 675 CASES ("OLD" AND "NEW") REFERRED TO THE PSYCHIATRIST BY THE DISPENSARY.

(Adults, 565; Children, 110; Males, 261; Females, 414.)

Per cent.	Clinic.
70.2	Medical
15.7	Pediatric
2.9	Gynecology
2.1	Dermatology
2.1	Pre-Clinic
1.7	Neurology
1.7	Eye
1.2	Ear, Nose, Throat
0.8	Admission office
0.4	Surgical
0.4	Genitourinary
0.4	Laboratory
Total 99.6	12 clinics (of a total of 18)

Based on our statistics, 14.6% of all new cases admitted to the medical clinic (about 1 out of every 7) were deemed preëminently psychiatric problems requiring treatment such as could only be given by a physician *with considerable psychiatric training.* Through close collaboration with the resident internists, studies of the "new" case material entering this medical clinic revealed nearly as many more cases which presented clinical problems that could not be understood and properly treated by a physician without *some* medicopsychiatric experience and training.

Incidence of Psychiatric Problems on the General Hospital Wards. During a period of $17\frac{1}{2}$ months (September 13, 1934, to March 30,

1936), there were admitted to the wards of the Colorado General Hospital a total of 6442 patients. These included 3347 women (1075 obstetrical cases), 1996 men and 1099 children. Of this number, 228 patients, 134 women, 77 men and 17 children (3.54% of the total, or 1 out of every 28 admissions), were regarded as psychiatric problems by the regular non-psychiatric visiting staff and were referred to the Psychiatric Liaison Department. These figures do not include the more *minor* personal maladjustments and personality reactions to and concomitant with admission to hospital, operation, child birth and the various somatic disease syndromes. However, we feel that these figures *do* represent the incidence of cases coming to this general hospital *that require the services of a physician well trained in psychiatric examination and therapeutic procedures.* For more detailed statistics showing the number of admissions to each hospital service, the number of psychiatric referrals therefrom, and the percentage of admissions so considered, see Table 2.

TABLE 2.—ANALYSIS OF SOURCE AND INCIDENCE PER HOSPITAL SERVICE.

Total admission to Colorado General Hospital (Sept. 13, 1934, to March 30, 1936) = 6442.		Of these there were referred to the Psychiatrist 228 cases, or 3.54% (*i. e.*, approx. 1 of every 28 admissions).	
General Hospital service or ward.	No. of admissions.	No. of cases referred to Psychiatrist.	Percentage of admissions referred to Psychiatrist.
1. Female medicine	1194	100	8.3
2. Male medicine	1016	63	6.2
3. Female surgery	1078	23	2.1
4. Male surgery	980	14	1.4
5. Obstetrics	1075	11	1.02
6. Pediatrics	1099	17	1.5
Total	6442	228	

Some Psychiatric Needs of the General Hospital and Four Points in Argument for Developing a Psychiatric Service Therein. If the tradition is true that a large percentage of the dispensary "medical shoppers" and "chronics" and patients *re*admitted to the general hospital for diagnostic studies are psychiatric problems, then the above statistics speak, without further ado, for the existence of a very pertinent and economically important need the general hospital has for a psychiatric service within its confines.

Aside from this, there is a still more important need that the general hospital has for developing facilities adequate to the understanding and treatment of the patient as a "mentally integrated whole." This need is connotated in the requirement that the teaching hospital promote medical research. Psychiatric research is increasingly calling upon the general physicians and specialists for assistance in understanding the "whole man." Conversely, the internist, surgeon or child research physician, who is endeavoring to arrive at the same understanding from a more traditional beginning,

is feeling a greater need for the psychiatrist's collaboration. The general hospital is certainly at present one of the most generally acceptable meeting places for all concerned in fulfilling an intention of this nature. Since it would seem that collaborative research of this bent is notably reliant on the advisability and possibility of the ingrowth of psychiatry in many general hospitals, the question then that makes itself immediately felt is—what psychiatric material is offered by the general hospital, and can the average general hospital afford a psychiatric development within its bounds? To answer this issue, four prerequisites must be considered: 1, A reasonable cross section of psychiatric material must be available; 2, the average accessibility of the personality of the cases for investigation must be conducive to adequate study; 3, a situation in which the concerted thought and coöperation of the various psychiatrists and non-psychiatrists is available for work with the case material; and, 4, a cost of operation of such a project not too great for the average medical school and general hospital.

1. *Type of Psychiatric Material Found in a General Hospital.* The general hospital offers an excellent cross section of psychiatric material as shown by the fact that of the first 745 cases examined and treated, nearly one-half (43.06 to 44.29%) manifested major psychotic disorders, over one-third (34.06%) showed psychoneurotic reactions of all types, and between one-sixth and one-seventh of the malbehavior was understandable, to a great extent, in terms of constitutional factors (Fig. 3).

2. *Accessibility of the Patients' Personalities to Investigation.* Irrespective of diagnosis, the peak of the age level curve of the General Hospital and Dispensary psychiatric patients is 21 to 30 years, whereas that of the patients in the Psychopathic Hospital is 31 to 40 years (Fig. 4). It might be inferred, therefore, that on the whole, the general hospital cases because of age are more plastic and therefore more accessible to psychiatric investigation and therapy. Then, too, and even more important, the psychiatric problems, on the whole, encountered in general hospital are qualitatively the same as found in the formal psychiatric clinic but are in our experience quantitatively less profound and incapacitating to the patient. It is, therefore, possible to study the patient more frequently in his "normal" habitat and surroundings; and to study and understand the fundamental behavior and functioning of the sick person, without as many interfering and misleading secondary features as go with an intensification of the disorder.

In our practice we see either the majority of the patients recover, remain in their respective reactions or get worse within a month, whereas in the identical but quantitatively more profound reactions usually found in psychopathic hospital, the time is measured in at least two to four times this term. Naturally, it would then seem, as in any other "experiment," that much can be learned, with a

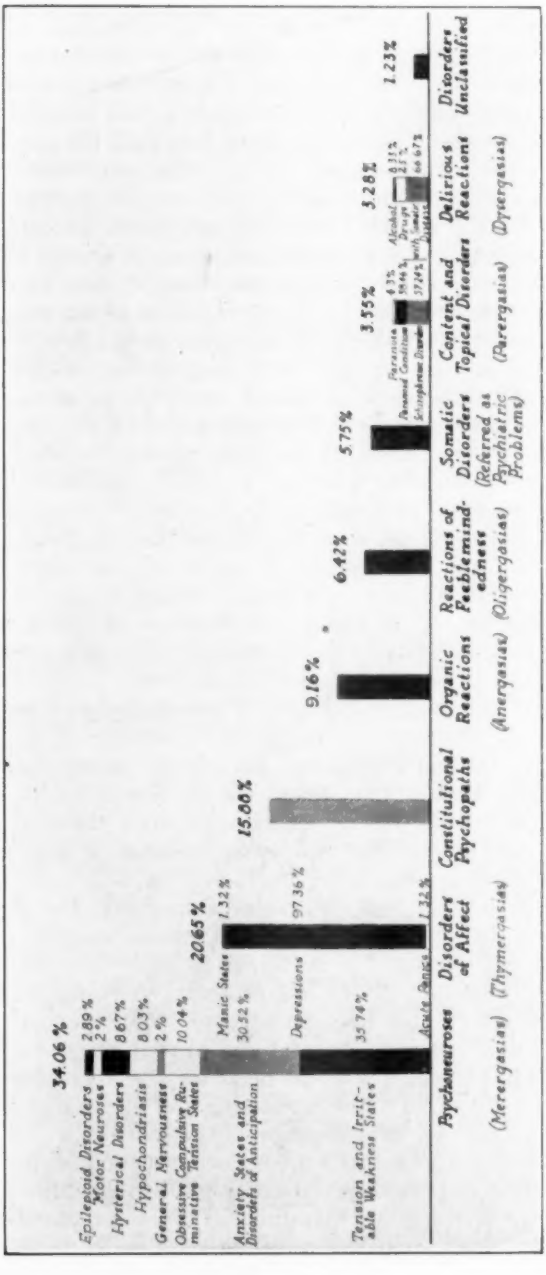

FIG. 3—Percentage comparison of "Reaction Types" manifested by the first 745 cases.

Note that incidence curve peak on General Hospital falls between ages 21 to 30 while that in Psychopathic Hospital occurs between ages 31 to 40.

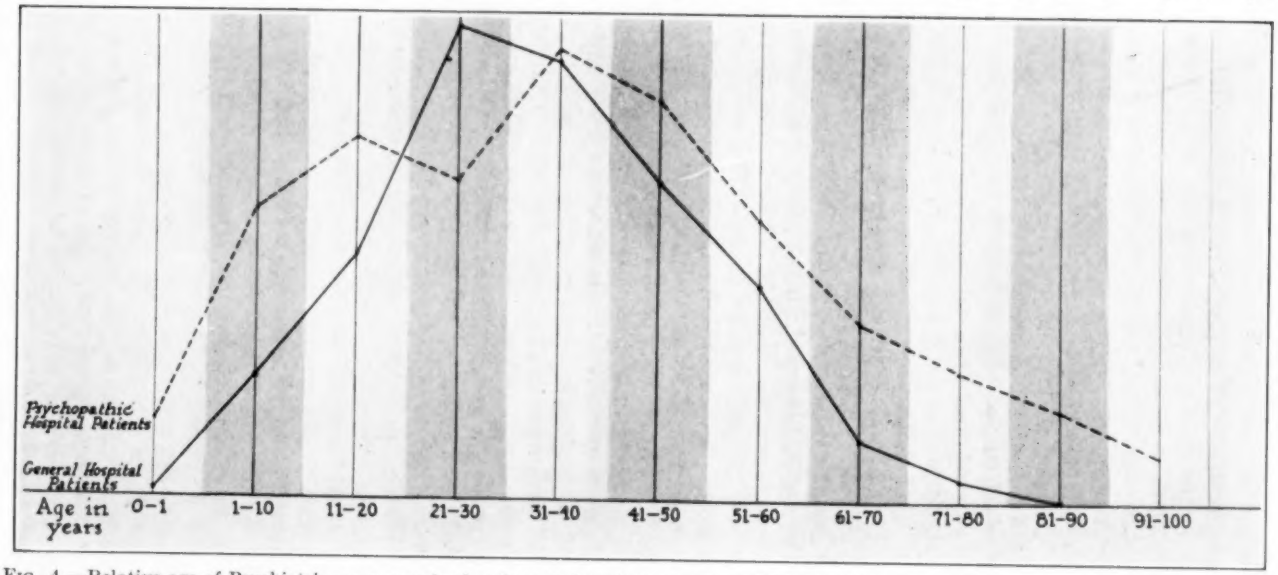

FIG. 4.—Relative age of Psychiatric cases examined and treated in Colorado General Hospital Wards and Dispensary (745) as compared with that of cases examined and treated in Colorado Psychopathic Hospital Wards and Dispensary (2266) from September 1934 to March 1, 1936.

minimum of time expenditure and floundering, from the psychiatric problems found in the general medical-surgical hospital. If a psychiatric hospital or clinic exists in conjunction with the general hospital, as is the case at the University of Colorado Medical Center, experience of undoubted value is offered the post-graduate psychiatric student or fellow, not only in understanding many of the psychiatric problems confronting us in psychiatry, but in practical training in the management of what would be considered office practice.

3. *The General Hospital; A Situation Conducive to the Collaborative Work of Psychiatrists and Non-psychiatrists.* The third item, the opportunity to work with case material hospitalized long enough to allow for concentrated research activity, is, at least in our situation to date, the most difficult one of all to attain. We have spent a great deal of time, and anticipate spending a great deal more, in leading the clinicians, the laboratory, and, most difficult of all, the people and governmental powers to realize that the admission and discharge rules of the hospital, the ordinary investigative and research studies of patients, must be broadened to encompass the problems of the "whole" man or woman or child admitted to the hospital or clinic. Research worth anything to medicine as a whole cannot be pulled out of a "cocked hat" by any one person. It must be the fruition of the combined efforts of all workers in all branches of medicine in a given institutional unit to satisfy the appetites whetted by the communal common sense understanding of the views and objectives of the others of the group. In this hospital and medical school aspirations of this nature are already gradually beginning to appear. We have every reason to believe that this attitude will gather intensity in our institution; and, that it can be developed in *any* general hospital.

4. *Operation Cost of a Department of Psychiatry in a General Hospital.* Finally, the value of such liaison developmental projects to psychiatry must depend ultimately on the formation of more such endeavors; and, therefore, on the financial outlay and running expenses necessary for a general hospital to maintain such a department. This item can be answered in one sentence. It cost the University of Colorado approximately $338 to furnish two unused laboratories as offices for the Department; and, excepting the salaries, the Psychiatric Liaison Department's expenses have averaged $28.85 per month.

Summary. 1. In a study of the "new" admissions to the outpatient department and to the wards of the Colorado General Hospital it has been shown that: (*a*) at least 1 out of every 28 admissions requires the services of a physician *well* trained in psychiatric diagnosis and treatment procedures.

(*b*) Of the new cases seen in the outpatient medical clinic, approximately 1 out of every 7 (14.6%) are predominantly psychia-

tric problems and as many more require psychiatric understanding and guidance.

(*c*) Between 6.2 and 8.3% of the admissions (about 1 out of every 13 admissions) to the medical wards of the general hospital conspicuously presented personality disorders which were the explanation of their disabilities.

2. The psychiatric needs of the general hospital are discussed as being, through their fulfillment, conducive to economy and better research along the lines of "physiology of the mentally integrated individual."

3. Four points are elucidated in favor of the development of psychiatric facilities within *more* general hospitals.

FREQUENT PSYCHIATRIC COMPLICATIONS IN GENERAL PRACTICE.*

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Through the gratifying increase of interest in psychiatric problems, much that is valuable has been written on this subject and has become a part of the common fund of medical information. The practising physician encounters far too many psychiatric problems in his daily work to permit him to refer all of them to the specialist in mental disorders, nor is this necessary or desirable for many of the more common problems to be discussed. We believe that a planned study of the personality factors involved in psychiatric disorders greatly enhances the likelihood of successful therapy, although we all know of highly gifted clinicians who deal more or less successfully with many of them without this aid. Everyone agrees that emotional, social, situational and kindred factors may cause complications in any somatic illness, but without some systematic knowledge it is difficult to deal efficiently with the mass of facts accumulated by investigation. As an aid to the practitioner or specialist in other fields we recommend the outlines for investigation of the past history, the family situation and heredity, the origin and development of the present illness, the underlying personality of the patient and the specific symptoms and signs of the various reaction types which may be found in any of the standard textbooks of psychiatry.[5] In this presentation I shall confine myself to a few of the psychiatric disorders most commonly encountered in the general practice of medicine.

Depression. One of the most common psychiatric disturbances seen is that of depression, which composes approximately 10% of

* Read before the Kansas City Academy of Medicine, Kansas City, Mo., November 20, 1936.

the cases admitted to the hospital (Colorado Psychopathic), and 20% of the cases seen by the Psychiatric Liaison Department (Colorado General Hospital). By depressions we mean those changes in mood varying from slight feelings of discouragement, sadness, futility, "the blues," to the major affective disorders which constitute separate clinical entities; involutional melancholia, endogenous depression associated with arteriosclerosis, manic-depressive psychoses, psychoneurotic depressions, and depressions in reaction to situations such as death of a loved one, financial loss, illness, personal defeats, or long continued stress and strain. We are all acquainted with the manifestations of the slightly depressed mood; with increased depression we see a growing aversion to activity, a stooped posture and dejected facial expression with wrinkled brow and drooping mouth. Spontaneity of speech is lost, the tone of voice is low and replies to questions are condensed as much as possible. Ordinary movements are performed only with heightened effort and more slowly than is usual. Answers to questions are delayed. The patient likes to be left alone, and expresses in various ways that he is downhearted, miserable, different from other people, lacks interest and is unable to think or act in the customary manner. He may complain of headache, dullness, confusion and inability to think, as well as of constipation and other gastro-intestinal complaints, insomnia (especially of the early-morning-waking-type which is very characteristic of this disorder), and loss of taste and appetite. Vague generalized somatic complaints referable to all organ systems suggest the presence of somatic delusions. In severe cases the patient will complain of feeling unreal or floating away, and of disordered function of various organs. If such delusions are present it is important that an expert consulting opinion be obtained, for a serious schizophrenic reaction may be ushered in by an initital depression with vague hypochondriacal complaints. In contrast to the toxic-organic disorders which are to be discussed later, we find that the sensorium of the depressive is only affected by the retardation. He is usually well oriented for time, place, person and situation; memory, retention and recall, counting and calculation, reading and current knowledge are not intrinsically impaired. Study of the complaint often suggests some degree of insight on the part of the patient. At times the depth of the delusions interferes markedly with judgment, as when ideas of personal wrong-doing, unworthiness, self-accusation, etc., are prominent. Paranoid delusional trends may be present. Often the mood is one of "impure" depression, *i. e.*, mixed with feelings of perplexity, irritability, petulance and suspiciousness. The most common admixture is that of apprehension with depression. Feelings of restlessness, tenseness, being under a strain, and uneasiness are indicative of a state of "tension." Tension, depression and anxiety are frequent concomitants of somatic disease and should be

treated by the practitioner with the same care that he devotes to the primary organic disease.

Before discussing details of treatment an extremely important topic must be considered, that of the prevention of suicide. It is the obligation of every physician to watch for it and to employ preventive measures. Any patient with depressive tendencies should be regarded as a suicidal risk. Dr. Ruth Fairbanks,[3] at the suggestion of Dr. Adolf Meyer at Phipp's Clinic, made an investigation of 100 cases who attempted suicide and found that 73% were depressives; while paranoid states, psychopathic personality, general paresis, epilepsy, chronic invalidism and recurrent manic excitement were represented by comparatively small ratios. A study of the case histories showed that the apparent motive for the suicidal attempt in a majority of the cases was a feeling of frustration or failure. A fear of insanity was often prominent, especially in cases in which there was a family history of mental illness. The frequent occurrence of suicides, depressions and alcoholism in the family histories was given special mention by the author. The attempt to escape from delusional persecution as well as from intolerable life situations were motives in a considerable number of these cases. The following danger signals may give the physician hints of a potential suicidal attempt: when the patient shows a definite tendency to self-condemnation and expresses feelings of futility, talks about the burden he is to his family and friends, desires to make a will, or desires to "get out of it all," the physician should employ special precautions such as having someone in constant attendance, removing all sharp instruments, medicines and drugs, and as far as possible ropes, cords, etc. Previous attempts are to be regarded as serious indicators since it has been shown statistically that such patients are especially dangerous, in spite of the myth that unsuccessful attempts are prophylactic. A patient, who is obviously tense, restless, worrisome, who attempts to pull away from attendants, or who shows overeagerness to join in activities outside of the house should be carefully watched. This can best be done in hospitals which are prepared to take care of such problems. An inexperienced personnel is totally inadequate to cope with the cleverness of a determined suicide. The physician in charge must employ special caution in determining when close surveillance should be relaxed. This is a very difficult question since treatment demands that restrictions should be as few as possible to avoid unnecessary rebellion on the part of the patient, and that occupational and other interests should be stimulated. Yet it is well known that many patients commit suicide during the convalescent period when there is every reason to believe that they are improving. Occasionally it seems as if a depressed patient will decide upon suicide and having made the decision is freed from many worries and therefore appears to be recovering rapidly.

The experienced physician will not be deluded by this too rapid change and will increase rather than decrease his vigilance. The special care of suicidal patients is a fascinating problem, and at the present time there is a growing body of informative literature on the subject. The persevering physician will be well rewarded for his pains, since affective disorders usually improve.

The decision as to whether a given patient should be treated as a potential suicide is not only most difficult but of the greatest importance. Many depressed neurotic patients consider or even speak of suicide by way of "escape," without seriously contemplating it. Here the physician must assume some responsibility in minimizing suicide-preventive measures, as their unnecessary use will seriously handicap the patient's recovery.

In general, whether a patient is suffering from a depressed mood secondary to another disorder or whether there is a "true" depression present, the patient should be placed in the most neutral environment possible, and protected against such annoyances as would increase the depression. Visits should be limited and carefully observed, since relatives often make futile attempts to cheer up the patient, or deliver very ill-considered and harmful advice on how to "snap out of it." Exhortations and arguments are especially to be avoided. Only short, cheerful, reassuring visiting should be allowed. In acute phases the physical surroundings should be as comfortable, quiet and non-stimulating as possible, in order to guard against the formation of delusions. Probing or investigative psychotherapy should be avoided. Interviews with the physician should be limited to short visits during which the patient should be made to feel that all his questions will be answered and that his illness is thoroughly understood. Very simple reassurance that mood disorders run their course and that the concomitant physical complaints are only a part of the emotional state is the foundation stone upon which the psychotherapy is built. As far as circumstances and the patient's intelligence permit, he should be cautiously "re-educated" as to his mental state and the damage of recurrences thereby diminished. As the patient shows increasing responsiveness to those talks, the range of activity should be increased in keeping with the abilities of the patient. It is important to remember that increasing privileges too rapidly, premature transfer from a comparatively neutral environment to a more stimulating one, or sudden withdrawal of sedatives without first tapering down the dose may cause the patient to relapse. A depressed patient is extremely critical of himself, and if he is encouraged to do more than he is able he will condemn himself for his failure, confirming the strong self-depreciatory trends already present. The danger of "probing" interviews, or the obtaining of "confessions" by strong urging has been mentioned; an insecure person may react with panic or resentment if the physician insists on penetrating his defense. In the latter

case, the patient may need a transfer of physicians in order to carry on the therapy. The tactful physician will encourage spontaneous discussions with the patient, utilizing the patient's initiative and interest as much as possible and avoiding painful or tabooed subjects until the depression clears up sufficiently to permit investigation. The material covered in these short reassuring interviews should be noted by the physician in order that it may be employed in future reconstruction of the development of the illness. The patient often gives extremely valuable leads to the sources of his preoccupation if the physician is willing to listen. Implicit in the patient-physician relationship is a mutual exchange; the patient gives his trust and confidence in the hope of receiving help; the physician should return reassurance and constructive formulations which will help the patient to meet his problems better from day to day. It is futile to attempt too much at one time since the depressed patient cannot appreciate his assets and will overemphasize his liabilities. With the lifting of the depressed mood, the physician can gradually introduce the topics of etiologic importance and begin such causal therapy as seems necessary or desirable.

The question of when to hospitalize the depressed patient is a highly individual one. Many mild depressions are being successfully handled through office interviews all over the country. The physician must realize his responsibility, however, and insist upon hospitalization 1, when he detects a potential suicide, 2, when the patient's environment mitigates against recovery, 3, when the patient is in danger of establishing a narrow, stereotyped behavior pattern (so-called "rut" formation), and 4, when the patient becomes a severe nursing problem requiring special attention to safeguard his health.

In the hospital, the activities of a patient can naturally be much better controlled than at home. In both places, however, monotony, fatigue and too great expectations are to be avoided. Since the rhythm of a depression varies, the patient may be encouraged by allowing him to do more on the days when he is feeling better, but these rhythms must be carefully explained in advance so that the patient will not be unduly discouraged when he finds himself unable to live up to yesterday's performance. He should be reassured, during the depressed periods, of eventful recovery. We find that walks, easy handicraft projects, reading of extremely light fiction, and superficial conversation are desirable for the more depressed periods. Card games, chess, dancing, athletic games of all types including lawn tennis, golf, croquet and the indoor competitive games can be utilized for the less depressed periods. Naturally the preferences of the individual patient are consulted in planning his daily activity. Rest periods should be provided but the patient should not be allowed to increase these without supervision, since ruminations are fostered by solitary inactivity.

Depressive patients and their relatives often ask the doctor about the value of travel. Patients in a "rut" formation may benefit by a change of scene; but, in general, experience shows that the depressed patient is accompanied by his illness regardless of his surroundings. The physician must have the courage to stand out against such suggestions and recommend real treatment. On the other hand, it must be recognized that under favorable conditions of companionship, finances and the patient's temperament or improving course, change of scene may prove to be a valuable therapeutic aid.

Close attention must be given to the physiologic functions of eating, digestion, elimination and sleep. Weight charts should be kept; nutrition may be maintained by urging the patient to eat or by employing spoon-feeding if necessary. Tonics for the stimulation of the appetite may be employed. Mild cathartics and laxatives are preferable to enemas since the latter may encourage preoccupation. Depressed patients often have an accompanying sleep difficulty usually of the early-morning-waking-type. A warm sedative tub of 1 to 2 hours' duration in the evening is often helpful in relieving this condition. If tension phenomena accompany the depression, small doses of barbital given at those times throughout the day when the tension and depression are at their height are a great aid. We have found barbital, gr. 1, to gr. $2\frac{1}{2}$ given 2 to 4 times a day very useful, although other barbituric acid derivatives may be substituted. Larger doses may lead to dullness, headaches and other subjective symptoms which add to the patient's confusion and feelings of inadequacy. Paraldehyde is excellent for immediate effect, but its vile taste and the prolonged odor surrounding the patient makes it impractical for the treatment of mild depressions. We do not encourage the use of bromides since uncontrolled ingestion leads to toxicity, especially in patients with systemic damage. It is often necessary to explain in detail to patients that the medicines being given them are not narcotics, and will not cause true addiction with the well-known withdrawal symptoms. We keep in mind, however, that there is a very real "psychic dependence" which is seen in those people with personality disorders who are helped to escape disagreeable realities by the use of a drug. Chronic alcoholism may be cited as an example of this condition. The physician is responsible for the complications following the use of drugs prescribed by him. He should recognize the toxic symptoms accompanying prolonged usage or overdosage. To aid physicians in their effort to prevent self-medication we believe that all these drugs should be sold only on a physician's prescription. Some states have laws regulating the sale of such drugs, but much more public education is necessary in order to obtain complete control.

Drugs are best administered in capsules, so that the identity and amounts are concealed and can be changed without comment from the patient. The dosage should be reduced frequently in a consistent

attempt to make the patient independent of his "crutch." It is desirable that patients who are in the hospital be independent of sedative medication before they are discharged.

My time is too short to discuss many other special treatment problems in connection with the depressions. If the principles laid down are utilized to the best advantage, the practitioner will find that he is able to handle these cases with more assurance and with greater success.

Anxiety. The group of symptoms composing the so-called "anxiety syndrome" was first described and named by Hecker in 1893, but was not generally recognized in this country until after the war. It has been known by many misleading terms such as: "disordered action of the heart," "D.A.H.," "irritable heart," "nervous heart," "effort syndrome," "soldier's heart," "neurocirculatory asthenia," and "functional cardiovascular disorder."

The picture presented varies in the number, character and intensity of the subjective and objective symptoms, according to the underlying personality structure of the patient. Naturally the manifestations of anxiety will be different in a psychoneurotic anxiety state than in an "anxiety state" which merely colors an underlying depressive or schizophrenic reaction. The basic disorder may also be due to brain destruction from head injury, paresis or arteriosclerosis. The anxiety may be associated with, although not directly caused by, some physical disease such as tuberculosis, diabetes or pernicious anemia. It always occurs in an individual who is inclined to be tense and uneasy, with rather sudden transient attacks varying in duration from a few seconds to an hour, and associated with palpitation, precordial discomfort, perspiration, difficulty in breathing, weakness, giddiness and even fainting. Although the symptoms mentioned obviously suggest disease of the various systems the physician can elicit the presence of the anxiety, *i. e.*, a fear of danger from within, a fear of illness or death, or only a feeling of uneasiness or impending danger. Through further questioning he will obtain information regarding difficulty in sleeping, anorexia, easy fatigue, or headache, often of the "band around the head" variety. We also find that the patient may be irritable, restless, losing weight, not feeling fit, or worried without knowing what about or why. A subjective feeling of being cold and unable to warm up is fairly frequent. Direct examination reveals ordinarily a tense, restless, uneasy, apprehensive person with cold clammy hands and feet, dry mouth, and labile pulse and blood pressure which are normal when the patient is asleep. The heart tends to hyperactivity with an occasional extrasystole, the colon may be tender to palpation, and the muscle and tendon reflexes frequently are hyperactive. In the series mentioned this syndrome occurs most often between the age of 21 to 25 and 36 to 40 years. The following table, worked out by Dr. Billings of the Psychiatric Liaison De-

partment of the University of Colorado School of Medicine and Hospitals, will be of value in differentiating between hyperthyroidism and the "anxiety syndrome"[1] (Table 1).

TABLE 1.—A FEW DIFFERENTIATIONS BETWEEN HYPERTHYROIDISM AND ANXIETY.*

Symptoms and signs.	Hyperthyroidism.	Anxiety states.
I. *Subjective symptoms.*		
1. Thermal response	Heat intolerance	Cold intolerance.
2. Drive and energy	Drive 4+, Energy 4+ — Easily exhausted	Drive 1+, Energy 0 — Constant fatigue.
3. Appetite	Increased	Decreased.
II. *Objective signs.*		
1. Weight	Initial gain; loss	No gain; loss.
2. Motility	Fine tremor	Coarse tremor.
3. Skin	Velvety and warm	Cool and moist.
4. Pulse rate	90 or more	Variable; usually less than 90; *normal* when at ease or asleep.
5. Pulse pressure	Increased†	No change.
6. Heat production	Increased	Usually normal.
7. B.M.R.	Constantly +20 or more	Erratic; usually normal.
8. Blood cholesterol	Decreased (normal 200)	Normal.

* Prepared by Edward G. Billings, M.D., Colorado General Hospital.
† Due to fall of diastolic pressure.

In treating a patient with an "anxiety syndrome" it is important to avoid the pitfalls of telling him that he should stop worrying, or that nothing is wrong, since he is unable to stop thinking about his trouble, and knows quite definitely that something *is* wrong. Neither is it profitable to say that the heart is in good condition and imply that it is not by giving advice regarding exercises or prescribing tonics. Pseudo-explanations, such as saying that the precordial sensations are due to gas in the stomach pressing up the diaphragm and crowding the heart, are also to be avoided, for any suggested treatment which does not deal with the actual etiology of the disorder will cause the patient to wander about seeking help, or discourage him further and thereby increase his depression, hypochondriasis and invalidism. The physician must be prepared to spend sufficient time to be sure of the diagnosis and of the actual development of the illness in that particular patient. This demand discourages some physicians since they feel that this procedure is too time-consuming. If, however, one balances the hour and a half required for a systematic examination, which will facilitate and shorten subsequent treatment interviews, against the many hours wasted in discouraging glandular and sedative medication, it will be seen that the long initial interview is entirely worthwhile. The anxiety and associated symptoms must be thought of as an expression of dysfunction of the whole person, and treatment should be directed against those factors which are the cause. Painstaking effort should be made to rule out any possible physical disease by taking a careful history, making a complete physical and laboratory examination, and studying the possibilities in the differential diag-

nosis. Then the environmental factors are examined. If, by changing occupation or home situation one can relieve the distress, it is obvious that these steps should be taken. If the cause is rooted in some malfunction of the personality, the complaints are studied in great detail in relation to the person who offers them. The serial picture obtained by intimate acquaintance with the patient's problems, assets, liabilities, and goals suggest specific treatment measures for that individual. The general types of these measures are known as aëration or ventilation, suggestion, reassurance, desensitization, and reëducation.

A few useful sedatives and hypnotic drugs should be discreetly employed only as a "crutch" along with other adjuncts (hydrotherapy, packs, and exercise) to help establish *rapport* and to break the vicious cycle of fears. As in depressions with tension, we have found that barbital in doses of 1 to 2 grs. given 2 or 3 times daily, is the most useful drug. Spastic constipation will be improved by *Tr. belladonna* (minims v–xii, t.i.d.), together with a regular diet and mineral oil. Hydrotherapy is extremely useful for relaxation and improves muscle and skin tone and general metabolism. It may consist of neutral tubs of 1 hour's duration given twice a day, or shower-baths employing both warm and cold water at varying pressures, or cold wet packs.

It is important to remember that psychotherapy begins with the entrance of the patient into the doctor's office. The long initial interview usually has a decidedly beneficial therapeutic effect, because it instils confidence in the patient and points out definitely the prospect of relief. Much of the ease with which a case will resolve itself depends upon the *rapport* established between the physician and patient, and the early understanding which the patient gains of himself. With adequate examination and explanation the majority of anxious patients will usually be able to see the real nature of their illness. If the physician will explain the relation of the symptoms to the underlying fears by giving common examples of visceral participation in emotional states such as anger, fright, or excitement, the patient will not concentrate his complaint upon the palpitation, precordial distress, shortness of breath, weakness, and so on. These symptoms become understandable manifestations of emotions which are common to all humanity. They are not disregarded as "imaginary" and therefore not respectable. When explained in a rational manner as the natural physiologic concomitants of an emotional state they lose their ominous significance as the possible forerunners of a dreaded "insanity." The diarrhea of soldiers during an attack; the polyuria during contests or examinations; the palpitation, perspiration, and choking, at sudden fright are common examples.

In view of the complexity of a patient's personality and his experiences it will usually be found that multiple factors are re-

sponsible for his illness. Situational factors dominant in the production of the illness must be altered if possible. Frequently, however, the patient must be taught to accept inevitable handicaps to modify his attitude toward them so that they are not active sources of conflict. He should be kept at his regular work if possible. When necessary the aid of the family should be enlisted, so that detrimental barriers to treatment may be removed. If the patient is unduly concerned or insecure about his work, it may be helpful to explain the nature of his illness to the employer so that the latter may lend sympathetic assistance. "Anxiety states" are eminently treatable, and the simple measures outlined above, when used with foresight and persistence, bring about a recovery in the great majority of cases.

Toxic-organic Reactions. Although in a series of cases seen at the Colorado General Hospital and Dispensary by the Psychiatric Liaison Department (Dr. E. G. Billings) the percentage of delirious reactions including those due to alcohol, drugs and somatic diseases was only 3.3%, there is reason to believe that the general practitioner sees a goodly number of them. The disorders complicating other diseases have received many names such as *symptomatic psychoses*, the *toxic-organic reactions*, the *exogenous reaction types*, the *dysergastic reaction types* (A. Meyer), and *mental symptoms in somatic ailments* (C. M. Campbell).

The delirious reactions are characterized by disorientation, hallucinations and a predominating affect of fear; they are closely connected with somatic conditions in that they are dependent upon, or associated with, intoxications by drugs or poisons, nutritional disturbances, circulatory phenomena and metabolic disorders. These disturbances produce temporary brain changes which are in the nature of edema or the obscure concomitants of fever and acidosis. The occurrence of delirium should not be considered merely incidental to the principal disease picture. It is a complication that may, and in a great percentage of cases does, interfere with the treatment of the presenting clinical problem. To say the least, it increases the suffering, prolongs the duration of the illness, and may necessitate special hospitalization of the patient; it may even be a disorganizing factor of such magnitude as to produce chronic invalidism and incompetency. The delirious patient, befuddled, disoriented, hearing threatening voices, misinterpreting situations, overwhelmed by misgivings and fear and given to action, is in acute danger of injuring himself and even of losing his life by jumping from a window. A very large percentage of deliria either are preventable or can be ameliorated if recognized early.

The delirious reactions are characterized by:

1, Clouding of consciousness and drowsiness; 2, Partial or complete disorientation leading to a state of bewilderment; 3, Dream-like or nightmare-like imaginative experiences when awake, with a tendency

to misinterpret the situation in keeping with the haziness and fearfulness; 4, Occurrence of vivid hallucinations and illusions of sight, hearing, tactile sensibility and position; 5, Frequently changing position; 6, Affect of fear and suspicion.

Etiologically the deliria may be grouped as follows:

1, Those due to exogenous toxins or poisons such as alcohol, opiates, bromides, barbiturates, and so on; 2, Those due to chronic cachectic states; 3, Those due to malnutrition, deficiency diseases (pellagra, avitaminosis, and so on) and metabolic disorders (hyperthyroidism, uremia, exhaustion states); 4, Those occurring as a part of an "organic reaction" such as in paresis or cerebral arteriosclerosis.

The general facts relative to a delirious reaction, as elicited on indirect examination (history of the illness from all sources), reveal that the onset of the condition usually is quite sudden and frequently makes its appearance at night, or when the patient's surroundings are changed. This onset is characterized by objective evidence that the patient is misinterpreting sounds, conditions and occurrences in his environment, has dream-like fancies and hallucinations and is partially or completely disoriented. The hallucinations usually are vivid and most frequently involve vision and hearing, although the skin may also be involved. If the above-mentioned features are not foremost, then the restlessness of the patient, his tendency to leave his bed and wander away and his reaction of annoyance, irritation, or fright may signal the beginning of such a reaction.

It can be seen from the foregoing that the treatment of the toxic psychoses requires knowledge of the whole domain of general medicine. Naturally, the specific therapeutic measures will be dictated by the type of infection or poisoning which is the basis of the psychosis. There are, however, certain general principles, which are applicable in the majority of cases:

1, Careful eliminative procedures are fundamental. Among these are catharsis, colonic irrigations, gastric lavage, attention to the fluid balance of the body and urinary excretion, and promotion of elimination *via* the skin.

2, An attempt should be made to control infection, if it is present and to eliminate foci of infection. Surgery often is required for the removal of infection and for the treatment of hyperthyroidism. Roentgen ray and radium may also prove of value. The administration of serums and vaccines may help to secure immunity against various infectious states.

3, The efficiency of the "support systems" should be bettered. For instance, cardiac stimulants and regulators should be utilized in case of actual or even threatened cardiac decompensation.

4, Dehydration and acidosis must be minimized and controlled. Routine dietetic and tonic treatment is required in the management

of the majority of psychoses of this group. Transfusions are indicated if the hemoglobin value is below 50%. They are extremely valuable and may be life-saving in hemorrhage, shock, certain poisonings, especially carbon monoxide, infectious diseases and severe secondary anemias.

5, If cerebral edema is present, spinal drainage and the cautious intravenous administration of hypertonic solutions, preferably 5% saline or 50% glucose, are indicated.

6, Sedation and its proper application with full appreciation of its dangers is important. Sedatives are of value in that they enable the patient to rest, but they should never be given for the sake of convenience in nursing care. Hydrotherapy and/or chemical sedation may be employed.

Of the hydrotherapeutic measures, the most helpful is the continuous or neutral tub. The temperature of the water should range from 97.6° (in case of hyperpyrexia) to 99° F. Care must be taken to keep the temperature in the tub room constant. The patient may be kept in a continuous tub for 1 to 24 hours without difficulty. The time element is solely dependent on the effect desired and the patient's physical status. The delirious patient's vegetative nervous system usually is unstable during his acute illness, and, therefore, shocks in the form of cold water must be avoided. Packs usually are contraindicated because the restraint involved promotes fear.

No hypnotic drugs should be given the patient during the day, but they are permissible at night when he is more apt to be disturbed. The type of hypnotic used depends on the type of delirium and the toxic agent causing the disorder. In general, a quickly acting, rapidly metabolized and rapidly eliminated drug, such as sodium amytal or paraldehyde is indicated. The hypnotic should be given in a large enough dose to cause sleep and should be administered before darkness, since the latter is prone to increase the patient's disorientation and fear. In beginning deliria, continuous sedation for a short time is helpful in preventing a prolonged reaction.

7, The nursing care is worthy of a great deal of careful consideration and requires understanding, ingenuity and skill. The patient must continually be reassured as to the intentions of the nurses and physicians. Furthermore, the management of the environment with the elimination of disconcerting shadows, sounds, and movements is necessary for the comfort and progress of the patient. He should be safeguarded from accident and suicide during the acute manifestations of the psychosis.

8, The verbal productions of the acutely ill patient may be of the greatest value in effecting an adequate personality adjustment, when the acute episode is past, and, therefore, should be noted carefully. This is particularly important in the deliria due to drug and alcohol addiction. In these cases, some analysis of the personality with

subsequent attempts at rebuilding is the only basic way of preventing recurrences.

9, All measures directed toward improving general hygiene are important. A regular daily schedule, written out and strictly adhered to, is useful, and as far as physical condition will permit, exercise and diversions (indoor and outdoor) should be arranged.

10, In many cases psychotherapy, as previously outlined, will prove the most potent of all therapeutic aids.

11, A prolonged period of convalescence is of great importance in preventing late sequelæ of the acute infections.

12, Follow-up care is essential.

13, Prevention is mentioned last although it should be first in the mind of the physician. Usually a medical man is not called until the delirium is present. A surgeon, however, often has it within his power to take steps to avoid a delirium. Apart from the avoidance of unnecessary and unwise administration of drugs, he must take into consideration the emotional factors involved in any surgical procedure. Dr. J. M. T. Finney of Baltimore, Maryland, speaking of "The Obligations and Responsibilities of the Surgeon,"[4] is an able exponent of the psychobiologic point of view in surgery. He reminds the surgeon that he should identify himself with the patient and remember that the fear, physical discomfort and pain, loss of consciousness, loss of time from one's regular occupation, may all combine "to cause the prospective patient many anxious moments and in certain cases, such an acute state of nervous shock and mental distress as seriously to affect the outcome of the operation."

The Organic Reaction Types. Among the many psychiatric problems encountered by the general practitioner, the organic reaction types are the most readily understandable. In almost all of these conditions, a definite organic lesion is present, and this lesion, if recognized, gives the physician a tangible explanation for the accompanying personality changes. In general, the organic reactions are chronic, being dependent on focal or diffuse, more or less permanent and intrinsic changes in the central nervous system. Obviously, transition states may exist between the delirious and the organic reaction types. Etiologically, the latter are associated with organic toxins, metabolic disturbances, syphilis, arteriosclerosis, neoplasm, trauma, senility, certain epilepsies, eclampsia and organic residuals of meningitis and encephalitis. While the clinical picture varies from case to case, and the etiology and duration of the diseases differ, the characteristic features of this type of disorder may be summarized as follows:

1, A definite organic change exists in the central nervous system. This may be in the nature of nutritional disturbance, neoplasm, inflammation, or degeneration. The motor and sensory reflexes are often disturbed, and these disturbances may lead to derangements of speech and equilibrium and to difficulty in writing and walking. Special laboratory and clinical procedures, such as study

of eye grounds and visual fields, examination of the spinal fluid and encephalography, are of value in diagnosing these conditions.

2, Personality changes are striking and are reflected both in the deterioration of ethical feelings and in the development of behavior patterns inconsistent with the individual's former habits. For example, a respectable person may become vulgar and obscene, and a frugal, conservative individual, extravagant and grandiose. On the other hand, the symptoms may represent an accentuation of the normal constitutional make-up. Thus, paranoid forms of senile deterioration may develop in persons who have always been suspicious and distrustful, and paresis may have a depressed or manic coloring, somewhat in accord with the patient's previous reaction pattern.

3, The affect is characterized by emotional instability with marked fluctuations in the mood. Thus, the individual may exhibit almost mercurial changes from joy to sorrow and back again.

4, Mental changes are quite characteristic and result in a decline in the patient's business and intellectual efficiency. The individual characteristically shows periods of confusion and bewilderment, difficulty in relating events which he has observed, fluctuations in his level of attention, defects in orientation, and retention, impairment of memory and comprehension, marked disturbance of judgment, and even delirium.

5, A large percentage of these conditions is entirely preventable. While this is obviously true in the case of the toxic organic types, it is equally true of most of the organic reaction types, especially all forms of central nervous system syphilis.

6, The prognosis varies according to the reaction types, but it is, in general, poor.

The recognition and treatment of these disorders is a part of the body of common medical knowledge and need not be further elaborated upon here[2].

By treating the patient as a human being rather than as a defective machine, the individual doctor will be rendering service which will reflect additional credit upon the medical profession. With the increased teaching of psychiatry in the better medical schools we can soon hope that every physician will become aware of the wealth of psychiatric problems in general medicine. We welcome the prospect of a closer union between psychiatry and general medicine for the mutual benefits of such a relationship will improve the standards of medical practice. It is with this thought in mind that the discussion of these disorders has been offered.

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THE IMPORTANCE OF SOFT TISSUE LESIONS IN ARTHRITIS.

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The usual cursory examination of the joints and periarticular structures in arthritis has resulted in an overvaluation of Roentgen ray findings. Routine roentgenograms, however, give details only of bone structure. Shadows of the soft tissues are, at best, poorly registered. Therefore they are usually disregarded and the diagnosis is based solely on the changes in bony articular structures.

The danger of such misinterpretation is realized if we consider that the finding of spurs is commonly accepted as evidence for the presence of osteoarthritis (hypertrophic arthritis). It was long ago pointed out by pathologists (Weichselbaum, Pommer, Schmorl) and recently confirmed by Keefer[3] and his associates, that degeneration of cartilage and osteophytes at the articular surfaces are present in over 80% of people past 40.

Clinical symptoms, however, develop in not more than 5 to 10%. Indeed, spurs are seen in most roentgenograms of people over middle age, who have never experienced trouble in their joints. Figures 1 and 2 show that Roentgen rays may give erroneous impressions even of bone lesions. Figure 1 was diagnosed by the roentgenologist of a large orthopedic hospital as an ankylosis of the patella.

In Figure 2 the patella was reported to be separated from the femur. Clinical examination, however, revealed the contrary to be true. After having satisfied himself that the patella in Figure 1 was, to his great surprise, freely moveable and in Figure 2 bound down evidently by adhesions, this roentgenologist discontinued to make a definite diagnosis and confined himself to describing impressions conveyed by the Roentgen ray pictures. The reservation of the final decision to the clinician is of benefit to both. It will be a great stimulus to develop advanced methods for registering the soft tissues.

A beginning was made in this direction by the inflation of air or other gases or by the injection of contrast media, like abrodil, into the joint cavity. These methods, under favorable circumstances, show changes in the soft tissues, like tears in the cartilages or hypertrophy of the synovial membrane. Unlike bone changes, soft tissue lesions are almost invariably associated with clinical symptoms. The greatest effort is indicated to advance our knowledge of their structure and behavior in health and disease.

The Synovial Tissue and the Normal Synovial Fluid. Until recently the synovial lining was commonly regarded to be a modified connective tissue devoid of specific function. Accordingly, normal synovial fluid was held to be a transudate with which soft tissue debris was admixed. The great variety in the number, size and shape of the synovial-lining cells and of the subsynovial tissue in

different sections of the joint was explained by the action of external factors like stress and pressure (Key[4]).

In 1919, however, Mayeda[7] demonstrated, chiefly in the knee joint of rabbits, special cells in well defined areas which contained Heidenhain and Altmann granules, regarded as indicating a secretion mechanism. Other cells gave a positive oxidase reaction and absorbed colloidal dyes and particles like India ink, iron and silver injected either intraärticularly or intravenously. In these areas, therefore, evidence of absorption and secretion was present.

Fisher[1] also found mucin in cells of synovial villi stained with thionin. My attempts to duplicate these findings with thionin were not successful. By modified toluidin blue staining of sections and scrapings of normal human knee joints, I found, chiefly in the synovial lining of the fat pads and the villi and fornix of the suprapatellar pouch, cells containing reddish-purple metachromatic granules (Kling[5h]). According to Metzner, these granules represent mucin or the precursor of mucin. Vaubel[9] confirmed the presence of these granules in cells of tissue cultures of synovial membrane of rabbits. He found the same variety of cells in the culture explanates as have been found *in vivo*. These variations are, therefore, not dependent on extraneous factors, but present a biological property of synovial tissue.

These morphologic and experimental studies have restored the synovial lining from the rôle of a passive connective tissue capsule, to that of an active organ, equipped with specific functions. The most important of these is the elaboration of mucin.

The Synovial Mucin. The presence of mucin in synovial fluids is demonstrated by a simple precipitation test: a drop of synovial fluid is let fall into a test tube with 2% acetic acid. A membrane is formed, which envelops the contents like a sac or tube (Fig. 5). Blood plasma, transudates and exudates give only various degrees of turbidity in the acetic acid.

On the basis of extensive studies (Kling[5a-g,m,6a,b] the following conclusions were drawn:

1. Mucin was found in each of 25 normal synovial fluids and in 94% of 200 synovial effusions of inflammatory or traumatic origin.

2. Mucin is responsible for the high viscosity of normal synovial fluid (from 10 to 20 times that of water) and for the wide fluctuation in the viscosity of effusions (from 1.6 to 102 times the viscosity of water, determined by the Hess viscosimeter). After precipitation of mucin, the viscosity of the supernatant fraction of synovial fluid drops to between 0.9 and 1.8.

3. Human synovial mucin is not a degeneration product from cartilage, because it does not markedly reduce copper sulphate, even after prolonged hydrolysis with hydrochloric acid, while chondromucin does so readily. It is not a tissue débris, because it does not redissolve in an excess of acetic acid and does not contain phosphorus-like nucleoprotein.

FIG. 1

FIG. 2

FIG. 1.—Roentgen ray diagnosis—ankylosis of the patella. Clinically, patella freely movable.

FIG. 2.—Roentgen ray diagnosis—patella free. Clinically, patella bound by adhesions.

FIG. 3.—Villus from normal synovial lining of human knee joint. Modified toluidine blue stain. Arrow points to 3 large cells filled with metachromatic purple and red granules (mucin).

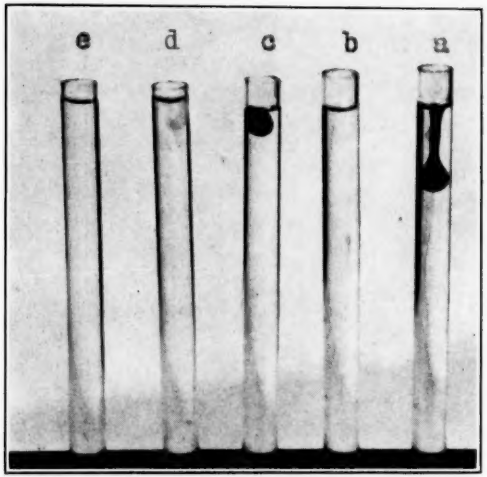

FIG. 4

FIG. 5

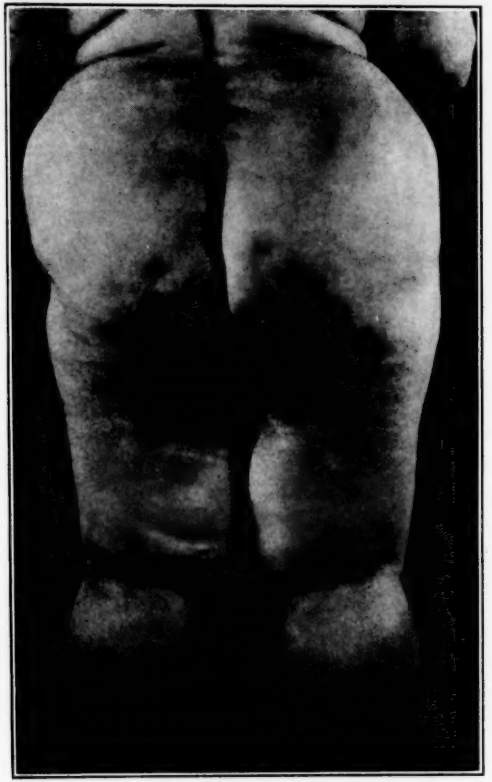

FIG. 6

FIG. 4.—Precipitation phenomenon of a drop of synovial fluid in 2% acetic acid. *A* and *C* show sac and tube formation. *D* shows a thin sac. *B* is a drop of pleural fluid, showing slight turbidity and no sac. *E* is a drop of transudate: the fluid remains entirely clear.

FIG. 5.—Illustrates acid binding power of synovial mucin. Addition of 10% hydrochloric acid resulted in tube formation which envelopes the acid.

FIG. 6.—Advanced case of juxtaarticular adiposa dolorosa. Notice the bulging fat pads at inner sides of knees which were hypersensitive to touch. Roentgen ray of knee joint was negative.

4. It is a physiologic product of specific activity as evidenced by morphologic studies and *in vitro*. Vaubel[9] found that the minute amounts of fluid in synovial tissue cultures gave positive sac and tube precipitation, as long as the cultures remained healthy. As soon as degeneration had set in, this test for mucin was negative.

5. Mucin is the chief component of normal synovial fluid and the one on which its physiologic action depends.

The Functions of Synovial Fluid. The main function of synovial fluid is the protection of articular surfaces by: 1, proper lubrication, secured by high viscosity, and 2, acid-binding power of the synovial mucin.

Cartilage is seriously damaged, even by short action of acids. It is exposed to the detrimental action of acid metabolites, which accumulate during inflammation. The acid-binding power of the synovial mucin is demonstrated by a simple experiment:

A small test tube is partly filled with synovial fluid; a drop of methyl orange is added. Most synovial fluids, being alkaline, take a yellow tint with this indicator. Several drops of 10% hydrochloric acid are let fall into the tube. The hydrochloric acid sinks, enveloped in a membrane-like covering which forms a tube and sac. While the rest of the fluid remains yellow, the contents of the tube and the sac change to red, which proves that they contain the hydrochloric acid (Fig. 6). The binding of the acid is permanent. The contents, even after prolonged standing do not take the uniform red color observed in the plasma, transudates or exudates. The chemical properties of the mucin are therefore a factor in the maintenance of the high degree of alkalinity observed even in inflammatory effusions and in the protection of articular cartilage from the acid metabolites.

3. A number of ferments were found in normal synovial fluids of cattle by Podkaminsky[8] such as amylase, lipase and a proteose. The proteolytic ferment is of special interest because it was observed also in tissue cultures, causing liquefaction of the media, proving it to be a product of the synovial tissue and not imported by the circulation. The presence of digestive ferments points to another protective property of synovial fluid, namely the digestion of the inflammatory or traumatic products, which precipitate within the joint cavity, such as fibrin, tissue débris, or fat particles.

The Bio-mechanical Significance of Joint Lubrication. Recently Jones[2] has experimentally proved on the stifle joints of horses the great importance of proper lubrication. The coefficient of friction amounted in dry joints to 14 times as much as in joints kept lubricated. In the latter, after 4 hours of mechanical motion, the joint surfaces were undamaged. In the dry joints, the internal semilunar cartilage and the condyle of the femur were worn down. The joint was steaming hot and grating was felt. Motion without lubrication has therefore produced changes encountered in some forms of chronic arthritis.

Fig. 6.—Advanced case of juxtaarticular adiposa dolorosa. Notice the bulging fat pads at inner sides of knees which were hypersensitive to touch. Roentgen ray of knee joint was negative.

The rich supply of vessels and capillaries in the synovial membrane serves not only to secure the exchange of fluids between circulation and joint cavity, but also to remove the heat produced by the motion.

The Reaction of Synovial Tissue to Injury and Inflammation and the Composition of Joint Effusions. Both trauma and inflammation induce pathologic changes, the degree of which depends on their severity, extent and duration. The wall is damaged in the first case mechanically; in the second by exudation and infiltration; the capsule is distended by hemorrhage or exudate from the circulation. Noxious metabolites are present both in the disintegrating hemathrosis and in the inflammatory exudate. Both contain fibrin and other particles, which irritate the joint tissues. The response of the synovial tissue is, therefore, alike in both injury and trauma, namely, hyperfunction of the intact parts resulting in an increased output of synovial fluid. A prolonged duration of the irritation results in hypertrophy of the synovial membrane (villous synovitis).

Both traumatic and inflammatory effusions, therefore contain: 1, elements from the synovial lining (mucin, ferments, and synovial lining cells); 2, elements from the circulation (blood cells, plasma, enzymes, antibodies or fibrin).

The quantitative and qualitative relation of these elements determines the character of the pathologic joint effusion. In acute virulent inflammation the exudate prevails. The quantity is large, the turbidity marked, and the vicosity is low. The cell count is high and polynuclear leukocytes prevail. In chronic synovitis, the synovial elements predominate. The fluid is visid, clear or contains suspended particles. The number of the synovial lining cells is increased.

Certain forms of arthritis have special features, such as high fibrin and globulin content in gonorrheal arthritis, abundance of débris in tuberculous arthritis and suspended particles in osteoarthritis.

The Clinical Value of Aspiration of Joint Effusions. A widespread prejudice against aspiration of joint effusion has retarded knowledge of joint lesions, has deprived the clinician of an excellent diagnostic aid and the patient of a beneficial therapeutic measure. In several thousand aspirations of traumatic and inflammatory (including tuberculous) joint effusions, I have not seen a single instance of an untoward effect. The therapeutic effect of evacuation of traumatic effusions is self-evident. Even in inflammatory effusion the temporary relief of distention and the removal of the toxic products are of decided benefit. I have frequently found on reaspiration the reaccumulated effusion to contain fewer cells or to have a lower viscosity than the original fluid. The therapeutic result of repeated aspiration was especially striking on gonorrheal arthritis.

Table 1 gives a review of a method of systematic examination of synovial effusions and the diagnostic significance of the tests.

TABLE 1.—SYSTEMATIC EXAMINATION OF JOINT EFFUSIONS.

Tests.	Significance.
1. Quantity	Large—in active and severe inflammation. Small—in mild, chronic arthritis.
2. Turbidity	(*a*) Homogeneous—depends on number of cells; (*b*) non-homogeneous—depends on suspended particles, such as fibrin or débris.
3. Reaction (pH or litmus)	Acid reaction in septic arthritis. Alkaline reaction on repeated aspiration indicates favorable prognosis.
4. Viscosity (Hess viscosimeter)	High viscosity in chronic arthritis. Low viscosity in acute inflammation or transudate.
5. Precipitation (2% acetic acid)	Sac and tube indicate mucin.
6. Fat in traumatic effusions (centrifuge)	Severe injuries to fat pads, menisci or intra-articular fracture.
7. Bilirubin	High icteric index (over 5) in traumatic. Low (under 5) in most inflammatory effusions.
8. Culture	(*a*) Septic arthritis: ready growth in routine cultures (streptococci, staphylococci, pneumococci, etc.); (*b*) acute gonorrheal arthritis: positive 10 to 25%; (*c*) tuberculous arthritis: cultures supplement the guinea-pig inoculation; often positive within 14 days; (*d*) chronic, atrophic and hypertrophic arthritis: routine cultures negative. Special method after prolonged incubation in 10 to 20% positive, chiefly for streptococci, staphylococci and diphtheroids. Etiological significance doubtful.
9. Animal inoculation	Standard method for tuberculosis.
10. Stained smears	Positive in septic arthritis, advanced tuberculosis and occasionally in acute gonorrhea.
11. Sections of suspended particles	For microscopic study of their nature and histologic structure.
12. Cell count	High (above 10,000 per c.mm.) in acute, severe stages, regardless of etiology. Low in mild, chronic and inactive conditions.
13. Differential count	(*a*) Predominance of neutrophils in acute stages, regardless of etiology; (*b*) lymphocytes, monocytes in chronic stages; (*c*) increase in synovial cells (over 10%) indicates hypertrophy of synovial wall (villus synovitis).
14. Wassermann	Clarifies etiology.
15. Gonococcus complement-fixation test	Positive in subacute and chronic gonorrheal arthritis.
16. Comparative sedimentation (blood and synovial fluid)	Indicates the condition of an affected joint and its rôle in polyarthritis.
17. Uric acid	Assists in differential diagnosis of gout.

The Periarticular Tissues. Careful examination often reveals that symptoms assumed to originate in the joints are due to changes in the periarticular structures, consisting of diffuse or localized contraction of the muscle, tenderness at the insertion of the tendons, and subcutaneous nodules. The inflammation of smaller joints is often combined with tenosynovitis.

Juxtaärticular Adiposis Dolorosa.[5n] Hypersensitivity and enlargement of the subcutaneous fat, especially around the knee (Fig. 6) and elbow joints, are frequently present in obese women past middle

age who complain of pain and stiffness in the extremities. A report of 112 cases of this condition which I have termed Juxtaärticular Adiposis Dolorosa, presents evidence of its important rôle as an etiologic factor in the development of osteoarthritis. This condition is usually associated with other periarticular changes of the soft tissues and circulatory disturbances, hypertension, varicose veins and acroparesthesia. Evidences also of hypo- and dsyfunction of the endocrine glands, especially ovaries, pituitary and thyroid, are found. The condition is usually overlooked in a superficial examination of the joints and the tenderness is erroneously assumed to originate in the articular structures, the more so, since in about 60% Roentgen rays show osteophytic changes in the articular surface. The latter are not more extensive, however, than should be expected in this age group.

From a therapeutic standpoint the diagnosis of periarticular changes is important. Stenosing tenosynovitis of the abductor longus and the extensor brevis tendons of the thumb is often diagnosed and futilely treated as arthritis of the wrist, while a simple operative procedure which frees the tendon from the stricture produces an instantaneous and permanent cure. The recent introduction of histamine by cataphoresis has proved to be of beneficial effect in the pathologic conditions of the periarticular structures (Kling [5-7]).

Summary. 1. Less speculation and more facts on joint pathology and physiology are needed for progress in research and therapy of arthritis and rheumatic conditions.

2. Bone changes as seen in routine roentgenograms are overemphasized and too little attention is given to the soft, intra- and extraärticular structures.

3. Morphologic, physiochemical studies and experiments show a dual structure and function of the synovial tissues; one part is a connective capsule for the binding of articulating bones. Interposed at the intraärticular surfaces are areas for the elaboration of the synovial fluid.

4. The function of normal synovial fluid is lubrication and protection of the joint surfaces.

5. Motion is the physiologic stimulus for the production of normal synovial fluid.

6. The function of normal synovial fluid depends on its content of mucin.

7. Mucin is a product of special cell activity and not of degeneration.

8. The biochemical importance of proper joint lubrication is stressed.

9. The therapeutic value of aspiration of traumatic and inflammatory effusions is pointed out.

10. The diagnostic significance of a systematic examination of joint effusions is reviewed.

11. Changes in the periarticular structures such as infiltration of the insertion of tendons, subcutaneous tissues and atrophy of muscles and tenosynovitis are frequently present and play an important rôle in the pathology of arthritis.

12. Hypersensitivity of the subcutaneous fat, especially at the knee and elbow joints (juxtaärticular adiposis dolorosa), is a frequent etiologic factor in the development of osteoarthritis in obese women past middle age.

13. In the therapy of soft tissue changes in arthritis, histamine cataphoresis has proven to be of value.

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THE FORMOL-GEL REACTION.

A Convenient Preliminary Test for Hyperglobulinemia.

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Sera of most patients with kala-azar rapidly form a solid, opaque white gel upon the addition of one or two drops of formalin.[12a,14] This phenomenon, commonly known as the formol-gel test, and used extensively for the diagnosis of kala-azar, depends upon the presence in the serum of increased amounts of globulin.[12b] A positive formol-gel reaction is obtained also in other diseases in which marked hyperglobulinemia may develop, notably in cases of multiple myeloma,[2,6,15] lymphogranuloma inguinale[16,6] and hepatic

cirrhosis[6]; and in occasional cases of malaria, leprosy, tuberculosis, subacute bacterial endocarditis, etc.[10,17]

In the present study, the usefulness of the formol-gel reaction has been investigated, not as a diagnostic test, but as a means for detecting hyperglobulinemia irrespective of etiology. Since its adequacy for this purpose would depend upon the consistency with which positive reactions are obtained with hyperglobulinemia, and negative reactions with normal serum globulin levels, we record here the results of the formol-gel test in 113 sera of which the content of total protein and of the several protein fractions was determined. Our data suggest that this simple reaction is consistent enough to serve as a convenient preliminary test for the detection of hyperglobulinemia of diverse origin.

It should be made clear, however, that prompt opaque-gel formation does not occur in the presence of only moderate hyperglobulinemia. In order to detect increases in serum globulin content of lesser magnitude than may occur in kala-azar, it was found necessary to make observations at the end of 24 hours and to regard as positive less striking changes in gelation and opacity than are obtained in kala-azar. This proved feasible since, with rare exceptions, sera with globulin contents within normal limits (obtained from normal subjects and from patients with a wide variety of diseases) showed no change 24 hours after addition of formol. A clinically practical schema for the quantitation of the formol-gel reaction is presented.

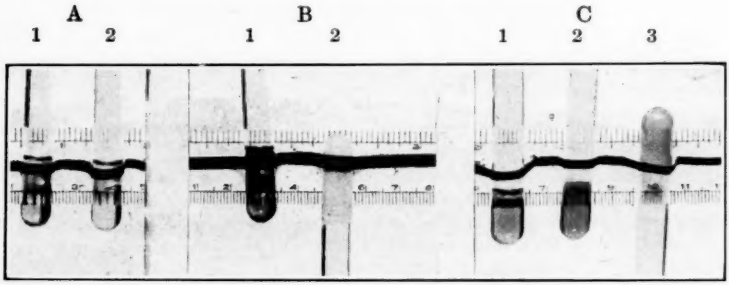

FIG. 1.—Illustrative formol-gel reactions. *A*, Normal serum (tot. prot., 6.3; alb., 4.6; glob., 1.8). No change in opacity or gelation after 24 hours. *B*, Case 27 (hepatic cirrhosis; tot. prot., 7.9; alb., 2.1; glob., 5.8). 4+ opacity and gelation after 5 minutes. *C*, Case 30 (hepatic cirrhosis; tot. prot., 7.2; alb., 2.4; glob., 4.8). No change after 5 minutes. 2+ opacity change and 3+ change in gelation after 2 hours. 3+ opacity and 4+ gelation after 24 hours.

Method. The formol-gel test is performed as follows: 1 cc. serum obtained from fasting patients is placed in a small test tube (8 mm. bore is a convenient size), 2 drops of approximately 40% formaldehyde solution are added, the whole is mixed and stoppered, and allowed to stand at room temperature. Since gelation and opacity may be due to different factors[3,6,8a] changes in both were recorded separately. Ordinarily, however,

the two phenomena occur together in positive sera, though in occasional cases only one or the other develops. Observations were made at arbitrarily selected periods of 5 minutes, 2 hours and 24 hours (Table 1, Fig. 1). This procedure proved better than attempting to record the results as the time which elapsed before specified alterations in opacity or gelation developed.

TABLE 1.—FORMOL-GEL REACTION IN 7 CASES OF MULTIPLE MYELOMA (M.M.), 16 CASES OF LYMPHOGRANULOMA INGUINALE (L.I.), 11 CASES OF CIRRHOSIS OF THE LIVER (C.L.), AND 12 MISCELLANEOUS CASES.

Case.	Diagnosis.	Serum proteins.				Formol-gel reaction of serum.					
						Gelation.			Opacity.		
		Total prot., %.	Albumin, %.	Globulin, %.	Euglobulin, %.	1/12	2 hours.	24	1/12	2 hours.	24
1	M.M.	11.1	2.3	8.8	0.4	4+	4+	4+	4+	4+	4+
2	M.M.	8.9	2.5	6.4	4.4	4+	4+	4+	4+	4+	4+
3	M.M.	9.2	3.1	6.1	2.3	4+	4+	4+	4+	4+	4+
4	M.M.	8.6	3.8	4.8	1.8	–	–	3+	–	1+	3+
5	M.M.	6.6	2.7	3.9	0.3	–	–	2+			
6	M.M.	6.3	3.1	3.2	0.6	–	–	–	–	–	–
7	M.M.	7.7	5.4	2.3	0.4	–	–	–	–	–	–
8	L.I.	11.1	3.3	7.8	3.2	4+	4+	4+	1+	2+	2+
9	L.I.	9.7	3.5	6.2	2.4	2+	4+	4+	2+	3+	3+
10	L.I.	9.9	3.8	6.1	2.3	3+	4+	4+	1+	2+	2+
11	L.I.	9.5	3.4	6.1	2.3	–	4+	4+	–	3+	4+
12	L.I.	9.1	3.1	6.0	2.4	2+	4+	4+	2+	2+	2+
13	L.I.	9.6	3.7	5.9	2.3	2+	4+	4+	1+	1+	1+
14	L.I.	9.1	3.5	5.6	2.9	–	4+	4+	±	4+	4+
15	L.I.	9.0	3.5	5.5	2.3	–	3+	4+	1+	2+	3+
16	L.I.	8.7	3.4	5.3	1.7	–	4+	4+	±	3+	4+
17	L.I.	8.6	3.6	5.0	1.7	–	4+	4+	±	2+	2+
18	L.I.	8.5	3.7	4.8	0.9	–	3+	4+	–	2+	4+
19	L.I.	8.1	3.3	4.8	1.5	–	1+	2+	–	–	2+
20	L.I.	8.6	3.9	4.7	1.7	–	2+	4+	–	–	2+
21	L.I.	8.0	3.5	4.5	1.5	–	4+	4+	1+	2+	2+
22	L.I.	7.5	4.1	3.4	0.9	–	–	–	–	–	–
23	L.I.	7.0	3.7	3.3	1.1	–	–	2+	–	–	1+
24	C.L.	9.5	2.2	7.3	0.5	–	4+	4+	1+	4+	4+
25	C.L.	8.4	2.4	6.0	2.1	1+	4+	4+	1+	4+	4+
26	C.L.	9.6	3.7	5.9	2.8	2+	4+	4+	±	1+	2+
27	C.L.	7.9	2.1	5.8	3.3	4+	4+	4+	4+	4+	4+
28	C.L.	7.4	1.8	5.6	2.2	–	4+	4+	1+	2+	3+
29	C.L.	7.2	2.2	5.0	1.7	–	3+	4+	–	2+	4+
30	C.L.	7.2	2.4	4.8	1.6	–	3+	4+	±	2+	3+
31	C.L.	7.4	2.8	4.6	1.3	–	–	4+	–	–	1+
32	C.L. (Banti's)	8.1	4.4	3.7	1.2	–	–	4+	–	–	4+
33	C.L. (Banti's)	6.6	3.3	3.3	0.7	–	–	–	–	–	–
34	C.L.	8.1	5.4	2.7	0.4	–	–	–	–	–	–
35	Syphilis	9.7	4.0	5.7	1.9	–	3+	3+	–	1+	2+
36	Undiagnosed	9.1	4.3	4.8	..	1+	3+	4+	2+	2+	2+
37	Undiagnosed	7.5	3.0	4.5	1.3	–	1+	3+	–	–	2+
38	Rheum. arthritis	9.0	4.6	4.4	1.1	–	–	4+	–	–	1+
39	Sarcoid (Boeck)	8.5	4.0	4.5	1.5	–	1+	3+	–	–	–
40	Hyper. cardiac	7.6	3.7	3.9	0.9	–	–	3+	–	–	–
41	Empyema	6.2	2.4	3.8	1.3	–	2+	3+	–	1+	2+
42	Ca., bone met.	7.6	4.0	3.6	..	–	–	–	–	–	–
43	Hepatitis	8.0	4.4	3.6	0.6	–	–	3+	–	–	–
44	Myxedema	7.0	3.6	3.4	0.9	–	–	3+	–	2+	2+
45	Hepatitis	6.9	4.1	2.8	0.5	–	–	–	–	–	–
46	Nephrosis	3.8	1.2	2.6	..	–	–	–	–	–	–

Changes in viscosity were recorded as follows: – or ±, no or questionable increase in viscosity; +, increased viscosity, definitely oily flow on tilting the tube; 2+, very viscous, a thick, slow-moving fluid; 3+, semisolid, no flow on inversion but jelly-like quiver on tapping the tube; 4+, solid. Care should be taken in reading 24-hour changes to break up the surface film which frequently forms. Changes in opacity were recorded as

follows: − or ±, no or questionable opalescence or haziness; +, opalescent, a faint haziness; 2+, translucent, milky, but freely transmitting light; 3+, semiopaque, cloudy but transmitting light; 4+, opaque. More accurate measurements of changes in viscosity and opacity by means of a viscometer and photometer seemed unnecessary for our purpose.

Except when associated with hyperglobulinemia, the presence of jaundice, anemia, lipemia, hypercholesterolemia, nitrogenous retention products or hemolysis does not result in positive reactions.* When lipemia is present, opacity changes are difficult to read, hence fasting samples should be used. If the original serum is not clear, a sample should be used as a control standard for comparison with formol-tested specimens. The temperature of the reaction, between 0 and 38° C., does not affect the results appreciably. The effects of prolonged tourniquet stasis and of dehydration were not studied.

Plasma should not be used, as we frequently obtained positive reactions with plasma in a variety of diseases when the corresponding serum was negative. It would appear that the presence of even moderately increased fibrinogen will cause the formol-gel reaction to become positive.

Total protein of the serum was determined by difference on 1 cc. samples, the micro-Kjeldahl technique being used for total nitrogen and Folin's method with Nesslerization for non-protein nitrogen. Serum protein partitions were carried out in duplicate on 0.5 cc. samples by Howe's method.

RESULTS. The results of the formol-gel test in 113 cases were tabulated as shown in Table 1, which includes representative observations in 46 cases, with associated serum protein values. It is apparent from Table 1 that a general correlation exists between positive formol-gel reactions and the level of total protein and globulin in the serum. An analysis of this correlation in our entire series of 113 observations is presented in Tables 2 and 3. It should be emphasized that for the purpose of this analysis a positive reaction is defined as a change in viscosity or opacity of 1+ or more after 24 hours.

1. *Relation of positive formol-gel test after 24 hours to total protein and globulin content of the serum.* As indicated in Table 2, 23 of 24 cases with total proteins of 8.5% or more showed definitely increased viscosity, and 22 of 24 developed changes in opacity in 24 hours. All sera with globulin contents of 4% or more showed an increase in viscosity; all but one developed some degree of opacity. These results suggest that marked hyperproteinemia and hyperglobulinemia can be detected satisfactorily by the formol-gel test.

Conversely, in sera with globulin levels below 3.4%, *i. e.*, in sera without hyperglobulinemia, the formol-gel test was consistently negative, only one slightly positive result being obtained in this group (3.3%, Case 23, Table 1). Positive reactions may be ob-

* This conclusion is supported by negative formol-gel tests obtained on more than 100 sera of patients with catarrhal jaundice, syphilis, anemias, nephritis, diabetes, neoplasms, infections and a variety of other diseases. These miscellaneous cases, which serve as an additional control group, are not included in our statistical analysis because serum proteins were not determined. Hyperglobulinemia, with positive formol-gel reactions, occasionally occurs in these diseases, however (Table 1).

tained, however, when the *total* serum protein is below the accepted upper limit of the normal range, 8%, if hyperglobulinemia is present (Table 3). Such sera are comparable to those with total protein levels above 8% in that they contain 3.4% or more globulin, but the total protein content is not increased because of a concomitant decrease in albumin.

TABLE 2.—A. CORRELATION BETWEEN PERCENTAGE OF TOTAL SERUM PROTEIN AND FORMOL-GEL REACTION. B. CORRELATION BETWEEN PERCENTAGE OF SERUM GLOBULIN AND FORMOL-GEL REACTION.

A. Total Serum Protein.

Total protein, %.		42 cases. <7.0.		36 cases. 7.0 to 8.0.		11 cases. 8.0 to 8.5.		24 cases. > 8.5 or more.	
		Pos.	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.
5 min.	Opacity	0	42	2	34	4	7	12	12
	Gelation	0	42	1	35	3	8	11	13
2 hrs.	Opacity	1	41	6	30	5	6	20	4
	Gelation	1	41	4	32	6	5	20	4
24 hrs.	Opacity	2	40	9	27	7	4	22	2
	Gelation	2	40	12	24	10	1	23	1

B. Serum Globulin.

Globulin, %.		52 cases. <3.4.		26 cases. 3.4 to 4.0.		35 cases. > 4.0 or more.	
		Pos.	Neg.	Pos.	Neg.	Pos.	Neg.
5 min.	Opacity	0	52	0	26	18	17
	Gelation	0	52	0	26	15	20
2 hrs.	Opacity	0	52	3	23	29	6
	Gelation	0	52	1	25	30	5
24 hrs.	Opacity	1	51	5	21	34	1
	Gelation	1	51	11	15	35	0

TABLE 3.—THE FORMOL-GEL TEST IN 113 SERA, TO SHOW THE INCIDENCE OF POSITIVE RESULTS WITH ELEVATED SERUM GLOBULIN, IRRESPECTIVE OF TOTAL SERUM PROTEIN LEVEL.

	Serum globulin, %	No. of cases.	Formol-gel reaction.	
			Pos.	Neg.
Total serum protein below 7%	<3.4	34	0	34
	3.4–4	8	3	5
	>4.0	0	0	0
Total serum protein, 7 to 8%	<3.4	17	1	16
	3.4–4	13	4	9
	>4.0	6	6	0
Total serum protein above 8%	<3.4	1	0	1
	3.4–4	5	4	1
	>4.0	29	29	0

Sera containing 3.4 to 4% globulin form an intermediate group, the recognition of which by means of the formol-gel test is uncertain. Only 11 of 26 cases in this group gave a positive reaction in 24 hours.

2. *Relation of (a) rapidity and (b) intensity of the formol-gel reaction to the globulin content of the serum.* As recorded in Table 2, positive reactions developing within 5 minutes or 2 hours occur, with few exceptions, only in sera with marked hyperproteinemia. Similarly, of 35 sera with globulin contents of 4% or over, 18 were positive in 5 minutes and 30 became positive in 2 hours. Only 5 such sera required more than 2 hours to develop positive reactions. Most

positive reactions obtained in sera with globulin contents between 3.4 and 4%, on the other hand, required more than 2 hours to develop. It would seem, therefore, that sera with globulin contents in the higher ranges develop the formol-gel reaction more rapidly; consequently, if positive reactions develop within 5 minutes, globulin contents exceeding 4% may be inferred.

Thus far we have considered the outcome of the formol-gel test only in terms of positive results, without making any distinction between 1+, 2+, 3+ or 4+ changes in gelation or opacity. If the results are analyzed as regards intensity of the reaction it becomes apparent that 3+ and 4+ reactions were obtained within 5 minutes only in sera containing well over 5% globulin. And as regards opacity changes, 3+ or 4+ reactions even at the end of 24 hours were obtained only in sera with globulins of 4.8% or over.

It is interesting to note that while practically all sera containing 4% or more of globulin developed opacity changes, some with very high globulin content did not give 3+ or 4+ reactions even at the end of 24 hours. There is, in fact, a considerable variation in the intensity of the opacity reaction obtained in sera containing approximately the same amount of globulin. These variations are so marked as to suggest that the quantity of globulin present is not the only factor responsible for opacity changes, but that qualitative differences in the several globulin fractions also play a rôle. There is experimental evidence in support of this view.[3,6,8a]

Discussion. It is apparent that the formol-gel reaction is a diagnostic aid only insofar as it is positive in diseases presenting hyperglobulinemia. Rapid formation of a solid opaque or semi-opaque gel does indicate the presence of such high globulin levels as are found chiefly in multiple myeloma, kala-azar, hepatic cirrhosis, lymphogranuloma inguinale and leprosy; and occasionally in other diseases.[1,4,8b,9,11,13] But moderate elevations in serum globulin, with 1+ or 2+ changes in gelation or opacity at the end of 24 hours are encountered in a variety of diseases, chiefly infectious, and are of little value in diagnosis.

The formol-gel reaction as a means of detecting hyperglobulinemia would seem to be useful in studies on the variation of serum proteins in disease. It may serve as a convenient preliminary method for selecting sera for protein fractionation, obviating the necessity for laborious analyses on negative sera. The test makes feasible the examination, on a more comprehensive scale than is ordinarily possible, of sera from patients with unexplained high sedimentation rates, hepatic disease, unexplained anemia, tuberculosis, etc. It should be emphasized, however, that the formol-gel test gives only an approximation of the degree of elevation in serum globulin content, and is obviously no substitute for serum protein fractionation unless facilities for the latter are unavailable.

Our data are in accord with the view that opaque-gel formation

depends upon the presence of an increase in the serum globulin fraction, irrespective of whether or not the total protein content is elevated. Since hyperglobulinemia is ordinarily the result chiefly of increases in the euglobulin fraction, as determined by Howe's method, the formol-gel reaction has been ascribed solely to hyper-*eu*globulinemia. Strongly positive results are obtained, however, in occasional sera with hyperglobulinemia due only to an increase in the pseudoglobulin fraction (Cases 1, 24, Table 1). We conclude, therefore, that opaque-gel formation is dependent upon the presence of "abnormal" globulins,* irrespective of whether their solubility characteristics with regard to sodium sulphate correspond with those of euglobulin or pseudoglobulin.

Concerning the chemical mechanism of the formol-gel test, nothing is known. The added formaldehyde presumably combines with the free NH_2 groups of the protein molecules.[5,7] But the precise nature of the changes in structure or in state of hydration that take place is, as yet, wholly obscure.

Summary. 1. The formol-gel test was performed in 113 sera of which the content of total protein and of the several protein fractions was determined. The results of the formol-gel reaction were quantitated according to a clinically practical schema in which changes in gelation and opacity were recorded at arbitrarily selected periods of 5 minutes, 2 hours and 24 hours. The rapidity and intensity of changes in gelation and opacity were correlated with the content of total protein, globulin and the several globulin fractions.

2. All but one of 24 sera with total proteins of 8.5% or more and all but one of 35 with globulin of 4% or more showed changes in viscosity and opacity within 24 hours. Conversely, all but one of 52 sera with globulin levels below 3.4% were negative after 24 hours. Sera containing 3.4 to 4% globulin could not be detected consistently by means of the formol-gel test. Sera with total proteins less than 8% gave positive results if hyperglobulinemia was present.

3. Of 35 sera with globulin contents of 4% or over, 30 became positive within 2 hours. Most positive reactions obtained in sera with globulin contents between 3.4% and 4%, on the other hand, required more than 2 hours to develop. Formation of an opaque or semiopaque-gel within 5 minutes occurred only in sera containing well over 5% globulin.

4. Our data suggest that the formol-gel reaction is consistent enough to serve as a convenient preliminary test for the detection

* "Abnormal" is used here to imply altered globulins apparently not present in normal serum. Reference has already been made to empirical and experimental evidence for qualitative differences in globulins, and to the probable causal relation of such differences to opacity changes. It is interesting to note in this connection that the minimal serum globulin level at which positive formol-gel reactions (as here defined) begin to appear corresponds closely with the accepted maximal level of serum globulins in normal persons.

of hyperglobulinemia of diverse origin. Possible applications of the test are considered. The formol-gel reaction is a diagnostic aid only insofar as it is positive in diseases presenting hyperglobulinemia.

5. Our results are in accord with the view that the formation of an opaque gel is due to qualitative as well as quantitative changes in the serum globulin fraction. The altered serum globulins responsible for opaque gel formation do not have solubility characteristics with respect to sodium sulphate which permit of their classification as euglobulin or pseudoglobulin, as determined by Howe's method.

Addendum.—While this article was in press, our attention was called to a publication by S. Hetényi (Verh. deut. Ges. inn. Med., **39**, 342, 1927) in which the formol-gel reaction was proposed as a test for hyperglobulinemia. No data are given. Very recently an excellent study by J. Bing (Acta Med. Scand., **91**, 336, 1937) has appeared, describing the formol-gel reaction as a general test for hyperglobulinemia. The conclusions of Hetényi, Gutman and Wise,[6] and Bing, are in general accord with ours as to the usefulness of the formol-gel reaction as a preliminary test for hyperglobulinemia, irrespective of etiology. For reasons stated in the text, we prefer to record the degree of opacity and gelation rather than that of gelation alone, as in the studies of Hetényi and Bing.

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BOOK REVIEWS AND NOTICES.

MEDICAL GREEK AND LATIN AT A GLANCE. By WALTER R. AGARD, B. LITT. (OXON.), Professor of Greek, University of Wisconsin. With an Introduction by C. H. BUNTING, M.D., Professor of Pathology, University of Wisconsin. Pp. 87 (every other page blank). Second edition, revised. New York: Paul B. Hoeber, Inc., 1937. Price, $1.50.

MANY medical terms sound so complicated to the lay ear that they have long been the subject of good-natured sarcasm in public utterances. Yet to the educated medical student such a word is not only usually self-explanatory; but, *multum in parvo*, conveys an extended meaning in a short space. With the unfortunate present day decline of the college man's "small Latin and less Greek" almost to the vanishing point, he is deprived of this royal road to medical terminology. This handbook has been prepared to lessen such damage. After a few pages of alphabet and pronunciation, it devotes 30 pages to words using frequently met prefixes and suffixes (such as "apathy," "ultralfitration," "stenosis," "sarcoma") and compound words (including such bastards as "costochondral," "visceroptosis"). The next 30 pages list alphabetically important medical words with their derivation from Latin and Greek, and the book concludes with classified lists of colors, adjectives, substances, numbers, chemicals, parts of the body and so on. Inexpensively prepared, the book cannot be too warmly recommended for every medical student. In fact, if not otherwise available, its possession is urged as indispensable.

E. K.

READING, WRITING AND SPEECH PROBLEMS IN CHILDREN. A Presentation of Certain Types of Disorders in the Development of the Language Faculty. By SAMUEL TORREY ORTON, M.D., former Professor of Neurology and Neuropathology, Columbia University. Pp. 215; 24 illustrations. New York: W. W. Norton & Co., Inc., 1937. Price, $2.00.

THIS study of disorders in the acquisition of the language faculty formed the basis of the author's recent Memorial Lecture. The meddlesome effort of some parents to overcome left-handedness in their children contributes to the development of certain speech disorders and merits condemnation. Among other problems discussed are troublesome forms of deafness, abnormal clumsiness and stuttering, all of which may hamper academic advancement or provoke emotional disorders.

As to matters of speech and manual dexterity: these are found to have a definitely restricted unilateral cerebral representation and it is shown that difficulties, the outcome of deviations in the process of establishing such unilateral brain superiority, may be prevented or removed by proper training.

There is no index, but since the work is not exclusively for physicians, the glossary supplementing the text will be found of infinite use to those parents and teachers who may become the fortunate possessors of this book.

N. Y.

SICKNESS AND INSURANCE. A Study of the Sickness Problem and Health Insurance. By HARRY ALVIN MILLIS, Professor of Economics, The University of Chicago. Pp. 166. Chicago: The University of Chicago Press, 1937. Price, $2.00.

THE problem of economic security against sickness becomes more acute as progress is made in medical science and as the popular demand for the benefits of medical knowledge increases. How to meet the costs of adequate

medical care is now a serious problem before the American people, to which much thought is being given by the medical profession, and by economists and sociologists. This contribution by a professor of economics in a large university discusses the nature and dimensions of the problem of sickness, the various attacks that have been made upon it through social insurance and what health insurance in proper coördination with public health service may do in solving the problem of sickness in the United States.

The extent and costs of sickness are not easily defined, as it requires drawing a distinction between what actually exists in terms of disabling illness and accident and what might be done to restore health, to increase efficiency and prolong life. The author concludes from his studies that the costs of sickness and accidents is a social problem ranking next to unemployment in importance, and in spite of all reasonable prevention, will remain a major problem.

The various forms of compulsory health insurance which are now in force in nearly all European countries are reviewed. The compulsory health insurance movement in the United States is then considered and a plan of health insurance for this country is suggested by the author. Professor Millis believes that "it is certain that compulsory health insurance will soon become a real issue in this country unless the existing legislation relative to old age and unemployment insurance is declared unconstitutional, or rapid advance is made in solving the problem of medical care upon a more acceptable basis."

He agrees with the statements that "without the coöperation of the medical profession, no system of practice can succeed" and "that more than 80 per cent of all the ailments for which people seek medical aid can be treated most cheaply and most satisfactorily by a family physician with what he can carry in a handbag." He suggests, therefore, that some plan of insurance should be devised which is limited in its scope to the major illnesses requiring hospitalization, elaborate study and specialist treatment. It is in such cases that there is urgent need of distributing costs. They constitute a relatively small percentage of the total, but account for approximately half of the outlays for medical care. The problems involved in such a plan are considered, and other parts of a comprehensive scheme for meeting in considerable measure the problem of sickness in the United States are briefly discussed.

The problem of medical care in this country is composed of economic, social and medical elements. The medical profession should therefore welcome contributions from their more theoretical collaborators among the economists and sociologists in attempts to solve these problems, especially as these collaborators are apt to weigh evidence more impartially and with more detachment than is usually possible by members of the medical profession. This contribution by Professor Millis is a clear, brief statement of a very complex problem, and a well thought out and constructive criticism of much that has been done and written on the subject. It is to be highly commended to those who have an interest in the health of the American people, of whom the members of the medical profession must take first place. G. R.

THE HISTORY OF THE ACUTE EXANTHEMATA. The Fitzpatrick Lectures for 1935 and 1936 delivered before the Royal College of Physicians of London. By J. D. ROLLESTON, M.A., M.D., F.R.C.P., F.S.A., Medical Superintendent, Western Fever Hospital, London. Pp. 114; illustrated. London: William Heinemann (Medical Books), Ltd., 1937. Price, 7s 6d.

CLOSELY associated with the acute exanthemata for 35 years at the Western Fever Hospital of London and long productively interested in the historic aspects of medicine, the author is well qualified to discourse on the

five diseases that comprise his subject. Smallpox, chickenpox, scarlet fever, measles and German measles are not only the most important acute exanthemata, but have the longest and most interesting history. Though known from ancient times, they have only been recognized as separate entities in surprisingly recent times, while their specific causative agents still remain in more or less obscurity. The ten portraits, which extend from Rhazes to Koplik, indicate the chronologic period covered; one regrets, by the way, that their provenance is not given. Clinicians, pediatrists, dermatologists, and all students of medicine should find satisfaction in this book. E. K.

THE PHYSIOLOGICAL BASIS OF MEDICAL PRACTICE. A University of Toronto Text in Applied Physiology. By CHARLES HERBERT BEST, M.A., M.D., D.Sc. (LOND.), F.R.S. (CANADA), F.R.C.P. (CANADA), Professor and Head of Department of Physiology; Associate Director of the Connaught Laboratories; Research Associate in the Banting-Best Department of Medical Research, University of Toronto, and NORMAN BURKE TAYLOR, M.D., F.R.S. (CANADA), F.R.C.S. (EDIN.), F.R.C.P. (CANADA), M.R.C.S. (ENG.), L.R.C.P. (LOND.), Professor of Physiology, University of Toronto. Pp. 1684; 398 illustrations and 1 colored plate. Baltimore: William Wood & Co., 1937. Price, $10.00.

THE distinguished author's contributions to endocrinology and experimental medicine would in themselves be sufficient to lead one to peruse this book with interest. Another item of interest therein is this latest example of a medical publishing trend, one which is especially noticeable in this country. More and more frequently do we see linked together in fresh combinations the old stereotyped subdivisions of medicine—in this case physiology, which is recognized as a science in its own right, and internal medicine. And so should they be, when it is recognized that much of today's physiology is either functional pathology or "medicine," much of today's pathology is abnormal physiology or medical etiology, pathogenesis and symptomatology; while biochemistry, from this point of view, is nothing but physiology or pathology. The point need not be labored further.

The present work, aiming to link together the laboratory and the clinic, regularly interprets the functional disturbances of common pathologic conditions. On the whole the interpretations are sound and satisfying and furnish, as the title states, a "Physiological Basis for Medical Practice." The reader will find discussions of such important symptoms and syndromes as polyuria, uremia, dyspnea, acidosis, edema, cyanosis, wound-shock, hemorrhage, hypertension, fever, etc., and of disease entities such as pneumonia, Bright's disease, various kinds of anemia and leukemia, angina pectoris, bronchiectasis and of many others.

The Reviewers are agreed that in the main the text is accurate and reliable and the selection of material judicious, with a wise elimination of unimportant work. Such linking of the resources of the clinical wards and physiologic laboratories cannot be otherwise than stimulating both to medical undergraduates and practitioners.

Having thus expressed our admiration for a noteworthy addition to medical literature, we may be permitted a few adverse criticisms. For instance, the blood and spleen chapters seem inadequate and not always exact: The spontaneous rhythmic contractions of the spleen are an old story and its reservoir function was known long before Barcroft and his party discovered it "more or less by accident;" the pale centers of the Malpighian follicles are rarely if every "germ centers;" many will not agree that experimental splenectomy "has yielded little definite information," or that clinically it should be limited to the diseases mentioned. Other instances need not be enlarged upon.

The physical makeup of the book is not pleasing. The paper is so thin and transparent that illustrations, especially photomicrographs and photographs of patients, are blurred almost as badly as in the newspapers. Figures like 27 and 268, for instance, would better not be shown. The absence of blackface type deprives the reader of a legitimate aid in finding divisions of the subjects. The Bibliography at the end of the book, instead of at the end of chapters, increases the difficulty of finding readily the references that one wants in connection with the text. A large bibliography at the end of a volume, to be sure, has its advantages; but these are largely lost if the references are offered chapter by chapter. The hundred pages of references fall between two stools. They are more numerous than required to support the statements in the text and not sufficiently numerous or well chosen to constitute a satisfactory bibliography of the many subjects covered. Granted the impossibility of satisfying everyone, still one gets the impression that the authors' personal lists of references have been augmented none too thoroughly from "standard" sources.

To recapitulate, the book is well worth while in its present form; it will undoubtedly be still more so in its next edition. E. K., B. L., I. Z.

PHYSIOLOGY IN HEALTH AND DISEASE. By CARL J. WIGGERS, M.D., Professor of Physiology in the School of Medicine of Western Reserve University, Cleveland, Ohio. Pp. 1124; 191 illustrations. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1937. Price, $9.00.

As stated by the publishers: "The discussions of many topics which were treated but briefly in the first edition have been expanded, including the biophysical principles, special senses, neurohumoral agents, pain and pulmonary affections. . . . Clinical material has been used in the discussion of physiological principles and the facts and conceptions established by experiment are applied to the analyses of clinical conditions."

This new edition contains well organized, well written, important information for the study and understanding of physiology in its relations to modern clinical medicine. The material is so organized as to make essential facts readily accessible. The book presents a happy combination of fundamental principles and practical applications. E. K.

AN INTRODUCTION TO MEDICAL SCIENCE. By WILLIAM BOYD, M.D., M.R.C.P. (EDIN.), F.R.C.P. (LOND.), DIPL. PSYCH., F.R.S. (CANADA), Professor of Pathology in the University of Manitoba; Pathologist to the Winnipeg General Hospital, Winnipeg, Canada. Pp. 307; 108 illustrations. Philadelphia: Lea & Febiger, 1937. Price, $3.50.

THIS department has often, and rightly, decried the use of short compends and textbooks abbreviated in an attempt to suit the modest demands and limited time of the medical student. Much better is it for him to own an adequate textbook that he has perforce become acquainted with, and that he can refer to later, even if he has not been able to read it from cover to cover during his medical school course. Approval of the present, volume, however, is not in the least inconsistent with the above viewpoint. As the author says in his Preface, "A little knowledge is a dangerous thing, but not if you know how little it is." (This, by the way, seems to the Reviewer to constitute an aphorism well worth permanent preservation in our literature.) Certainly, the nurse, technician and premedical student for whom the book is chiefly intended should not be in danger of thinking that they have acquired sufficient knowledge of the subjects treated to

equip them for their life work. On the other hand, presented by one who knows his subject and who is able to write clearly and forcibly about it, this little book gives perspectives of correlations between lesions and symptoms that often permit a better comprehension of the essential processes of disease than is possible in the necessarily more detailed conventional textbooks. One who is contemplating or beginning medical studies, or a patient who wishes to understand more about himself must often wonder "what it is all about, not seeing the wood for the trees," again in the words of the Preface. This attempt should put him on the right track.

The greater part of the book follows the conventional plan of a textbook of pathology: Part I, General Principles on the nature and various causes of disease, and general body reactions (*i. e.*, Etiology and General Pathology); Part II, diseases of different parts of the body, considered in much the same order as in Special Pathology, but in quite a different way. A short Part III, Practical Applications, deals with the Prevention of Disease and the Nurse and the Laboratory.

We hope that the book will be widely disseminated among those whom it is designed to serve. We know of none that supplies this real need as well as this one does. E. K.

A Hand-book of Ocular Therapeutics. By Sanford R. Gifford, M.A., M.D., F.A.C.S., Professor of Ophthalmology, Northwestern University Medical School, Chicago; Attending Ophthalmologist, Passavant, Wesley Memorial, Evanston and Cook County Hospitals. Pp. 341; 60 illustrations. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1937. Price, $3.75.

The demand for this excellent text on Ocular Therapeutics has necessitated a second edition, which includes a number of new procedures that have appeared in the literature in the past 4 years. It is an extremely useful book for both the general practitioner and the ophthalmologist. F. A.

Endocrinology. Clinical Application and Treatment. By August A. Werner, M.D., F.A.C.P., Assistant Professor of Internal Medicine, St. Louis University School of Medicine; Associate Physician, St. Mary's Group of Hospitals, etc. Pp. 672; 265 illustrations. Philadelphia: Lea & Febiger, 1937. Price, $8.50.

This clinical endocrinology is written in a direct, lucid manner, and describes the underlying physiological principles in a way that is adequate for an understanding of diseases and their treatment. Many case histories are given of illustrative types. It should be a very useful book for the general practitioner. It is a very scientific, clinical presentation of endocrinology, almost completely eliminating endocrine fantasies, and containing few individual viewpoints on which the Reviewer would differ.

In a book of this type, it would seem better to omit some of the descriptions of uncorroborated and debatable publications, pathological conditions not proved to involve endocrines and experimental work not directly applicable to human disease; because if such matters are discussed, it would seem advisable to present them in all their intricacies from all standpoints, and that can be done only in large systems or in books on separate endocrine organs. In a single volume on all endocrines, errors of omission would seem preferable. However, the space allotted to such matters is very small and theories and personal views are clearly separated from concrete facts; consequently no intelligent reader should be confused.

The physical makeup of the book is very attractive. It should fill a real need in treating of clinical endocrinology in the compass of a single volume. I. Z.

DISEASES OF THE NEWBORN. By ABRAHAM TOW, M.D., Adjunct Professor of Pediatrics, New York Polyclinic Hospital and Post-Graduate Medical School; Assistant Adjunct Pediatrician of the Abraham Jacobi Division for Children of the Lenox Hill Hospital, etc. Pp. 477; 53 illustrations. New York: Oxford University Press, 1937. (No price given.)

THIS volume offers mainly a rather adequate digest of the literature pertaining to those conditions affecting the newly born infant. The subject matter is almost entirely presented in an impersonal way—most of the treatments resembling the brief abstracts to be found in the abstract section of a journal. Unfortunately there are very few references to the author's experiences and no analyses of cases or groups of conditions and results which might have been included for the sake of prognosis. Other recent volumes concerned with the New Born period have been less encyclopedic but have evinced more originality of treatment and have offered far more in the way of personal experience. It is significant that practically all of the illustrations are drawn from the literature. The author adopts a sound, conservative position on all debatable matters. This is to be commended but the didactic statements would be more forceful if supported by case analyses and hospital statistics. E. T., JR.

A HUNDRED YEARS OF MEDICINE. By WYNDHAM E. B. LLOYD, M.A. (CANTAB.), M.R.C.S. (ENG.), D.P.H. (ENG.). Pp. 344. London: Gerald Duckworth & Co., Ltd., 1936. Price, 15/.

THIS is one of Duckworth's 100-year series, other volumes having already appeared on Psychology, Inland Transport, Anthropology and English Government. In the first part is presented the study of medicine 100 years ago; in the second and longest, the scientific discoveries of the past century, and in the third, the organization of public health. The author was obviously faced with such unmanageable abundance of material, that he feared unwieldy details on the one hand, unreadable excessive condensation on the other. He therefore determined on arbitrary selection of those items that would be more interesting to and easily understood by the English layman and appears to have selected wisely. Anyone who has digested this book will be well informed on the progress of medicine in the past century. E. K.

TRAUMA AND DISEASE. Edited by LEOPOLD BRAHDY, B.S., M.D., Physician in Charge of Industrial Diseases and Accidents in the Office of the Corporation Counsel of the City of New York, and SAMUEL KAHN, B.S., M.D., Medical Examiner in the Bureau of Workmen's Compensation of the Department of Labor, State of New York, New York City (25 Contributors). Pp. 613; illustrated. Cloth $7.50. Philadelphia: Lea & Febiger, 1937. Price, $7.50.

THIS book is timely in view of the increasing compensation given to workers injured during their work and the increasing awards made for liability accidents. The editors have written from their extensive experience the first chapter on trauma in the etiology of disease. Thereafter follow 16 chapters by men who are outstanding in their field, each discussing trauma in its relation to disease in a single part of the body. For example the chapter on trauma and heart disease, written by P. D. White and R. E. Glendy, discusses the general principles, etiologic relationships, structural changes and disorders of function of the heart resulting from trauma. Then follows a series of illustrative cases with a brief but comprehensive discussion. Various authors have appended bibliographies.

The book is excellent as a reference for those who are confronted with the problems of the relationship between trauma and disease. It should be invaluable to physicians dealing with compensation or liability insurance. It is undoubtedly the outstanding work of its kind. L. F.

THE PSYCHOLOGY OF EATING. By LEWIS ROBERT WOLBERG, M.D. Pp. 321. New York: Robert M. McBride & Co., 1936. Price, $3.00.

THE author, a psychiatrist at King's Park State Hospital, New York, who also lectures to the nurses there on dietetics, begins his preface with no mean claim. He states that the book "Is a complete scientific system of eating which discusses the need for a new dietary point of view. It is a book which reviews comprehensively medical, social and psychological aspects of diet. It is a practical book which will help every normal person to construct a balanced menu for the utmost enjoyment of health and efficient living. And it will permit one to secure new standards in dietary efficiency without sacrifice or self-deprivation, without robbing oneself of the zest and appetite pleasures inherent in good foods." Written directly to the prospective dietist, the book records many sound observations and reflections in commonly understandable terms and in an easy style, reminiscent of some American anti-faddist literature. Guided by the principal "Because science speaks an unknown tongue many people fall victims to the blandishments of the food faddist," the author gives concrete rules for dieting in overweight and underweight and in various disease conditions; but always with a sufficient background of *raison-dêtre* to appeal to the intelligent. E. K.

CATARACT. ITS PREVENTIVE AND MEDICAL TREATMENT. For Specialists, General Practitioners and Students. By A. EDWARD DAVIS, A.M., M.D., Formerly Professor of Ophthalmology, New York Post-Graduate Medical School and Hospital (Columbia University), etc. Pp. 161; 11 charts. Philadelphia: F. A. Davis Company, 1937. Price, $3.00.

IT is unfortunate that the statistics reported in this book, to substantiate the author's claim for the successful use of lens-protein in the treatment of cataracts, are not convincing. Until the treatment has received confirmation by other workers, it hardly merits presentation in the form of a book. F. A.

NEW BOOKS.

The Normal Encephalogram. By LEO M. DAVIDOFF, M.D., Assistant Professor of Neurology in the College of Physicians and Surgeons, Columbia University; Attending Neurological Surgeon to the Neurological Institute of New York, and CORNELIUS G. DYKE, M.D., Assistant Professor of Radiology in the College of Physicians and Surgeons, Columbia University; Assistant Director, in the Department of Radiology of the Neurological Institute of New York, New York City. Pp. 224; 149 illustrations. Philadelphia: Lea & Febiger, 1937. Price, $5.50.

Failure of the Heart and Circulation. By TERENCE EAST, M.A., D.M., F.R.C.P., Physician, King's College Hospital and Woolwich Memorial Hospital. Pp. 130. London: John Bale, Sons & Curnow, Ltd., 1937. Price, 2/6d.

Public Medical Services. A Survey of Tax-supported Medical Care in the United States. By MICHAEL M. DAVIS. Pp. 170. Chicago: The University of Chicago Press, 1937. Price, $1.50.

The Patient and the Weather, Vol. IV, Part 1. By WILLIAM F. PETERSEN, M.D., with the assistance of MARGARET E. MILLIKEN, S.M., Organic Disease. Cardio-vascular-renal Disease, including a Chapter on Experimental Endocarditis by ALEXANDER J. NEDZEL, M.D., Associate Professor in the Department of Pathology, Bacteriology and Public Health, University of Illinois, College of Medicine, Chicago. Pp. 663 (lithographed); 443 illustrations. Ann. Arbor: Edwards Brothers, Inc., 1937. Price, $10.00.

Physicians and Medical Care. By ESTHER LUCILE BROWN, Department of Statistics, Russell Sage Foundation. Pp. 202. New York: Russell Sage Foundation, 1937. Price, 75c.

Clinical Reviews of the Pittsburgh Diagnostic Clinic. Guideposts to Medical Diagnosis and Treatment. Eight Contributors. Edited by H. M. MARGOLIS, B.S., M.D., F.A.C.P. Pp. 552; 6 figures, 5 charts and 4 tables. New York: Paul B. Hoeber, Inc., 1937. Price, $5.50.

Sindrome Adiposo-Genital. By DR. LUIS VIAMONTE CUERVO. Pp. 62. Habana: Seoane, Fernándex Cía, 1937.

Dr. Bodo Otto and the Medical Background of the American Revolution. By JAMES E. GIBSON. Pp. 345; illustrated. Springfield, Ill.: Charles C Thomas, 1937. Price, $4.00.

The International Medical Annual. Fifty-fifth Year, 1937. A Year Book of Treatment and Practitioner's Index. Thirty-four Contributors. Editors: H. LETHEBY TIDY, M.A., M.D. (OXON.), F.R.C.P., and A. RENDLE SHORT, M.D., B.S., B.Sc., F.R.C.S. Pp. 605; 89 text illustrations, and 68 plates (some in color). Baltimore: William Wood & Co., 1937. Price, $6.00.

The Practice of Ionization. By J. NEWTON DYSON, M.R.C.S. (ENG.), L.R.C.P. (LOND.). With a Foreword by ELKIN P. CUMBERBATCH, M.A., B.M. (OXON.), D.R.M.E. (CAMB.), F.R.C.P. Pp. 178; 9 illustrations. London: Henry Kimpton, 1936. Price, 6/.

NEW EDITIONS.

A Textbook of Embryology. By HARVEY ERNEST JORDAN, A.M., PH.D., Professor of Histology and Embryology, University of Virginia, and JAMES ERNEST KINDRED, M.A., PH.D., Associate Professor of Histology and Embryology, University of Virginia. Pp. 613; 473 text illustrations, 33 plates. Third Edition. New York: D. Appleton-Century Company, Inc., 1937. Price, $6.50.

Important in this edition are many improved illustrations and textual additions under the topics of hemopoiesis, lymphatics, lung, sex determination, and anomalies.

Mikromethodik. Quantitative Bestimmung der Harn-, Blut- und Organbestandteile in Kleinen Mengen für Klinische und Experimentelle Zwecke. By LUDWIG PINCUSSEN. Pp. 193; 31 illustrations. Leipzig: Franz Deuticke, 1937. Price, M. 5.

PROGRESS
OF
MEDICAL SCIENCE

SURGERY.

UNDER THE CHARGE OF
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NITROUS OXIDE–OXYGEN ANESTHESIA AND ANOXIA.

Nitrous oxide-oxygen has been generally considered as one of the safest of anesthetic agents. It is because of this that it has been commonly employed for patients whose condition is not especially good. It has, in fact, often been used as the anesthetic of choice in "bad risk patients." It has frequently been employed in the presence of hypotension, either acute or chronic, for it has been generally taught that nitrous oxide and oxygen anesthesia causes a rise in the systolic blood pressure. Even if this does occur, the resultant effects may be such as seriously to impair functions which may already have been impaired by the lesion requiring anesthesia and operation. The frequent casual suggestion for "just a whiff of gas" indicates a lack of consideration for the possible dangers in the use of this gas. Its use is widespread for minor surgical conditions as well as in situations where it is difficult to watch the patient such as in fluoroscopic reduction of fractures and in obstetrical practice.

That this anesthetic is not as safe as most of us have believed is now becoming apparent. The dangers from nitrous oxide have been stated frequently.[1–3,5,6,8,10,12,15,17,18,23,31] The most important are those associated with anoxemia. The induction of the anesthetic state with nitrous oxide depends largely, if not completely, on the production of anoxemia with a resulting decreased oxygenation of the tissues. Henderson, Brown and Lucas,[16] Leake and Hertzman,[19] and Greene and Curry[14] have indicated that the anesthetic effect of nitrous oxide is due chiefly to the anoxemia which it causes. That there may be some

narcotic effect is not denied, but it is a well known fact that in order to get deep anesthesia with nitrous oxide and oxygen, it is necessary to decrease the oxygen concentration to a level at which definite cyanosis is apparent. After a period of anoxemia, however, it is frequently possible to maintain fair anesthesia with a decreased concentration of nitrous oxide. Even at this period, however, the concentration of oxygen which can be used and still maintain anesthesia with moderately efficient relaxation is at the critical level for oxygenation of tissues and below the concentration normally available to the organism in the air. Greene and Curry[14] concluded that anesthesia with nitrous oxide and oxygen depended more on the decrease in saturation of oxygen in the blood than on increase of saturation of nitrous oxide. Henderson, Brown and Lucas[16] tested the concept of Bert[4] and Martin[22] that nitrous oxide alone could produce anesthesia if the pressure were increased, but were unable to verify the conclusions of these authors. Henderson and his associates[16] placed rabbits in a specially constructed tank containing a mixture of 84% nitrous oxide and 16% oxygen at a pressure of 2 atmospheres without producing anesthesia.

Anoxemia is, as is well known, commonly associated with nitrous-oxide-oxygen anesthesia. When the patient is kept "pink," as Yandall Henderson has insisted he should be, unless there is an associated anemia, the dangers from this gas mixture are minimized. The difficulty of maintaining a good color and obtaining the required depth of anesthesia is obvious. Despite the fact that the average surgeon looks upon cyanosis as a warning sign that the patient is receiving too little oxygen, there are those who feel that cyanosis, during nitrous oxide-oxygen anesthesia, is not only to be expected but is necessary.[21] Raginsky and Bourne,[26] however, state that it is possible to produce anesthesia in man without cyanosis. In addition to the anoxemia from nitrous oxide-oxygen anesthesia, there is usually an additional anoxia resulting from the pre-operative administration of depressant drugs. The use of morphine pre-operatively has become nearly universal. Morphine is known to depress respiration. In addition to its depressant action on pulmonary ventilation, morphine has a tendency to produce tissue anoxia. Not only does morphine tend to depress oxygenation in the organism, but Shute and Davis[28] demonstrated that morphine given to mothers had an asphyxial effect on the newborn infant and scopolamine supplemented this action.

There are additional methods by which the anoxemia of nitrous oxide and oxygen anesthesia may still further affect function. The stimulation of the medullary centers by oxygen want may slow cardiac activity and increase peripheral vasoconstriction. The increased peripheral resistance may impede blood flow and lead to a further oxygen deficit to the tissues. This may be especially true when the original condition requiring anesthesia has already seriously influenced blood flow in the periphery. The cumulative effects of an oxygen deficit from an impaired blood flow prior to anesthesia, and a further reduction during anesthetization with a mixture providing an insufficient or minimal amount of oxygen may be sufficient to cause a serious breakdown of normal functions.

Many reports of deaths during nitrous oxide-oxygen anesthesia are

to be found in the literature. That less sudden, but often as serious effects may follow anesthetization is not so generally recognized. That following nitrous oxide-oxygen administration certain disorders such as hysteria, coma, disorientation and various motor disturbances occurred has long been known. In fact, in his work, published in 1800, Sit Humphrey Davy[9] reported the following: "That single doses, nevertheless, are capable of producing permanent effects in some constitutions is evident, as well from the hysterical cases as from some of the details, particularly that of Mr. M. M. Coates." The detail referred to is a description of the subjective effects on Mr. Coates after breathing nitrous oxide and indicated that Mr. Coates was quite irritable and unsteady, so much so that for 6 or 7 days he was handicapped in his work and was mildly hyperexcitable for over a fortnight.

Undoubtedly, should one very carefully study postanesthetic cases, with the thought of learning of minor nervous disorders, it is quite likely that many could be found to be related to the anesthesia, and it is quite possible that many unexplained deaths might be attributed to the anesthetic agent.

The most carefully studied series of cases with regard to sequelæ of nitrous oxide-oxygen anesthesia is that of Courville.[7] In a series of 9 cases which terminated fatally, Courville was able to find evidence, by a study of microscopic sections, of definite cerebral cell damage. The damage consisted of degenerative cortical changes of varying degree. During anesthesia in most of the cases there was some difficulty, either in the nature of deep cyanosis or a period of respiratory arrest. The postoperative symptoms were somewhat varied, but hyperthermia was present in all the cases which terminated fatally. Motor weakness, coma, convulsions, flaccidity, and increase in respiratory rate were common findings. The postanesthetic survival period varied from 40 hours to 26 days.

In addition to the 9 cases which died, Courville[7] also reported 4 cases which recovered, 2 completely, and 2 in which residual mental changes persisted.

In 2 of the instances a definite defect was found in the machine which was used for administering the gas mixture so that no oxygen was given, and in other instances, the gas used contained an excess of free nitrogen. The importance of an efficient apparatus and the highest purity of the gas mixture is, therefore, of the greatest importance.

The cases reported by Lowenberg, Waggoner, and Zbinden,[20] and by Schreiber and Gates[27] were quite similar to those of Courville.[7] The postanesthetic sequelæ were so much like those of Courville that there can be no doubt but that the mechanism was a similar one. These three papers, we believe, are of the greatest significance and should be read by all those who still believe that this gas mixture is the safest anesthetic in the hands of the professional anesthetist.

The possible cause of these disturbances is to be sought in anoxemia of the brain tissue. Added weight is given to this concept by the work of Gildea and Cobb,[13] who in experimental animals produced brain lesions similar to those found by Courville in his patients. Apparently, it is necessary that a greater insult be given than is offered by the anoxemia from a carefully administered uneventful nitrous oxide-oxygen

anesthesia. Either the oxygen unsaturation must be extreme as in the cases where pure nitrous oxide was given, or where respiratory difficulties ensued; or the ability of the tissues to utilize oxygen must be impaired; or the actual oxygen carrying apparatus must be at fault, as in cases with anemia; or the ability of the pulmonary tissue to transfer oxygen must be defective, as in Courville's first case who had a lung abscess, as well as in one in the series of Lowenberg, Waggoner and Zbinden; or the reduction in the blood flow must be so great as to lead to a serious oxygen deficit. The possibility of materials other than nitrous oxide having been administered as impurities is, of course, present. Free nitrogen as an impurity should tend only to increase the anoxemia. If other impurities were present which might act similarly to carbon monoxide in binding available hemoglobin, a train of events such as described by Courville,[7] Lowenberg, *et al.*,[20] and Schreiber and Gates[27] might ensue. We know of no suggestion that nitrous oxide will form a stable compound with hemoglobin. Should nitric oxide be present, such a compound would form. Nitric oxide hemoglobin is quite stable and has been shown by Drabkin and Austin[11] to give a curve similar to carbon monoxide hemoglobin when studied spectrophotometrically. The possibility of saturation with nitric oxide, if such were present, would be increased during phases of oxygen lack, since in the presence of oxygen, higher oxides of nitrogen would be formed. These oxides are likewise toxic, and are irritating. Pflesser[25] found that nitric oxide was toxic in smaller doses than the dioxide so that when nitric oxide was administered as an impurity, adequate oxygen would act to reduce the toxicity. Nitric oxide might be expected to be formed in the preparation of nitrous oxide from ammonium nitrate, and carbon monoxide likewise is a possibility if organic impurities are present in the ammonium nitrate.[29] Not only is the formation of nitric oxide a possibility, but Palkin[24] reports the presence of this compound in small amounts in samples of nitrous oxide tested by the Bureau of Chemistry of the United States Department of Agriculture. The actual amount of nitric oxide necessary to produce toxic effects need not be great if there is already deficient oxygenation, since the action of this compound would be expected not only further to decrease the oxygen-carrying capacity but to depress the tissue respiration as well.

Whether the sequelæ of nitrous oxide-oxygen anesthesia reported by Courville,[7] Lowenberg, Waggoner and Zbinden,[20] and Schreiber and Gates,[27] are due to lack of oxygen or to a toxic substance in the gas mixture is an unsolved problem. Were it not for the occasional case in which the period of anoxemia is very short, the relationship between anoxemia and the brain injury found might be adequate to explain the difficulty. Marked anoxemia and arrest in respiration are not uncommon, yet the occurrence of brain damage is rare even after a stormy anesthetization. The relationship of blood flow, especially cerebral blood flow during the period of anoxia, must have an important bearing on the postanesthetic sequelæ. An efficient blood flow during the period of anoxia will probably offset the low oxygen saturation, while an anoxia further accentuated by an impaired blood flow will accentuate the tissue changes. The sequelæ described by the above authors are so dramatic that they cannot be overlooked, but their relationship to

anesthesia may be overlooked. Toxic materials have been found only in small amounts in commercial nitrous oxide. If anoxemia were absent during anesthesia, the toxic material which may be present, namely nitric oxide, would be less toxic if toxic at all, since it would be readily oxidized to the higher oxides. It appears quite possible that anoxemia and the toxic impurities present may combine to cause the disturbance noted by Courville,[7] Lowenberg, Waggoner and Zbinden[20] and by Schreiber and Gates.[27]

Nitrous oxide-oxygen anesthesia is frequently given under a variety of conditions, and by inexperienced anesthetists. It has been said that 97% of anesthetizations are given by individuals not medically trained,[30] and, of course, some of the remaining 3% are given by medical men and dentists not trained in anesthesia. The choice of the anesthetic and the method and manner of its administration are important considerations and are frequently more important than the operation which is to be done. Anesthesia has widened the scope of surgery; the willingness of many surgeons and patients to trust anesthesia to lay hands has definitely hindered the progress of anesthesia.

The margin between life and death under anesthesia is narrow enough to cause us to think seriously about the problem. Evidence of irreparable tissue damage as a result of anesthesia should indicate that we should be even more on our guard. In experienced hands nitrous oxide-oxygen is a dangerous anesthetic—the danger is surely not minimized by trusting this agent to individuals inexperienced in the physiologic, pharmacologic and pathologic aspects of anesthesia.

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OPHTHALMOLOGY.

UNDER THE CHARGE OF
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THE ETIOLOGY OF RECURRENT UVEITIS. A REVIEW OF EXPERIMENTAL STUDIES.

THE determination of the cause of an individual case of iridocyclitis or uveitis, particularly of recurrent type, is often, if not usually, extremely difficult. In the absence of definitely demonstrable syphilis, tuberculosis, or blood stream infection by staphylococci, streptococci, meningococci and the like, which latter usually produce single and not recurrent attacks of uveitis, the ocular disease is usually ascribed, in this country at least, to focal infection. At times these foci of infection can be demonstrated readily, and their removal has a favorable effect on the course of the ocular disease. At other times no obvious foci can be found. At times removal of foci and treatment with specific, autogenous, or nonspecific vaccines has little permanent effect on the course of the disease or on its recurrence. The reasons for this failure of therapy are not clear. In any case of uveitis, whether due to syphilis, tuberculosis, or focal infection, the mechanism of the recurrent attacks is not well understood. In some cases of syphilitic and tuberculous uveitis, the specific organisms can be demonstrated in the tissues of the eye. In most cases, however, organisms cannot be found in the ocular tissues.

In the early years of the theory of focal infection, various workers attempted to demonstrate the bacterial metastatic character of iritis and uveitis. In 1915, Rosenow[12] reported that, in a large group of animals injected intravenously with various organisms, particularly strains of streptococci, 48 animals had developed lesions of the eyes. He stated: "It must not be supposed that the occurrence of these lesions is accidental because they appear to occur commonly only after injections of strains as isolated in rheumatic arthritis and myositis (17%) and in herpes zoster (15%) while after injections of strains from appendicitis, ulcers of the stomach, cholecystitis and erythema nodosum, eye lesions are extremely rare." Rosenow then proposed his theory of "elective localization" of streptococci in which it is assumed that, under certain conditions of growth in foci or in culture, the streptococci develop "specific affinity for certain tissues."

Experimentally, iritis can be produced in animals by the direct injection of organisms into the anterior chamber. According to A. L. Brown, Koske in 1905 produced ocular inflammation in rabbits by injecting into the anterior chamber living *B. subtilis*, *B. prodigiosus*,

and staphylococci. Iritis will also occur in the homolateral eye following the injection of pathogenic organisms into the internal carotid artery. Iritis develops at times also after intravenous injection of living bacteria, as demonstrated by Rosenow and others. Brown states that it has been reported also after the intravenous administration of yeasts (Stoch), of filtrates of ferment-producing bacteria (Guillery), and of toxin from *B. prodigiosus* (Wood). Benedict states that Brown and Irons produced iritis in rabbits by intravenous injections of streptococci, *B. mucosus capsulatus* (Friedländer), *B. pyocyaneus*, and gonococci, as a result of which they concluded that bacteria reach the eye through the circulating blood and can be recovered from the eyes in which iritis has occurred. It was necessary, however, to inject sufficient organisms to produce a septicemia.

Apparently, it was not until after the reports of Rosenow in 1914 and 1915 that attempts were made to utilize, for experimental intravenous injections, organisms derived from humans with iritis or uveitis. In 1916, Irons, E. V. L. Brown and Nadler[8] reported the results of intravenous injections into rabbits of hemolytic streptococci cultured from a chronic dacryocystitis in a patient with acute iritis. Typical iridocyclitis developed in 3 of 4 animals injected. Organisms obtained from the sac one month later caused iritis in 2 of 4 rabbits. Later cultures from the sac failed to cause iritis in any of 22 rabbits injected. Apparently, "the invasive power of the organism for special tissues" had been changed during residence in the focus, as it was proved to be changed in animal passage and also in subcultures.

In 1919, Lewis[10] reported the production of iritis in a rabbit by the injection into the blood stream of a culture of *Streptococcus viridans* grown from a periapical infection in a patient with acute iritis. The same organism was recovered on culture of a section of the rabbit's iris. Lewis stated: "This experiment proves absolutely for the first time, as far as I know, the selective affinity of the organisms found in dental root abscesses for the special structure which had been affected in the individual from which the tooth was taken."

In 1921, Meisser and Gardner reported the experimental production of iritis in rabbits through two animal passages with a streptococcus isolated from an infected tooth in a case of acute iritis. Benedict,[2] in 1921, studied the effects of the intravenous injection into rabbits of green-producing streptococci obtained from foci of infection in 14 patients with iritis and uveitis. Five of the patients had acute iritis. Organisms obtained from 4 of these 5 patients produced iritis in rabbits. Nine of the patients had chronic and recurrent iritis or chronic uveitis. Organisms obtained from these patients failed to produce iritis in rabbits. He stated his belief "that iritis is produced by bacteria arising from foci of infection around the roots of teeth and in the tonsils, that it is an inflammatory reaction brought about by the presence of bacteria in the tissues of the iris carried to the iris by the blood stream from the foci of infection, that such bacteria have the ability to grow and do grow in such environments." He stated further: "Iritis of focal infection origin is a myositis caused by an organism that at some period of its growth may cause iritis and at other periods inflammation of some other muscle. . . . This affinity for iris tissue becomes a function of the organism spontaneously or may be acquired by growing on

iris tissue . . . . this affinity for the iris is easily lost by the organism when grown in different environments . . . . it will change its affinity for special structural tissue or even lose its virulency to a marked extent." The possibility of the streptococcus acquiring an affinity for the uveal tract by growing on iris tissue is disputed by Brown, who found that growing the streptococci in uveal tissue attenuated the virulence of the organism for the uveal tract, though he states that Zanettin obtained the opposite result.

In 1923, Haden[7] reported that lesions of the eyes occurred in 68% of 66 rabbits injected intravenously with freshly isolated cultures of streptococci obtained from the teeth of patients suffering from metastatic infections of the eye. In a control group of 169 rabbits injected with cultures obtained from patients without eye lesions, inflammation of the eyes developed in only 14.8%. Haden stated also that he had noted recurrent attacks in the injected rabbits.

In 1927, in summarizing his experiences of many years in the study of focal infections, Rosenow[12a] stated with particular reference to lesions of the eye: "Relief from symptoms following removal of foci of infection, while good evidence of causal relationship, still leaves open the question whether the lesions in the eye were the result of localization of bacteria or of their toxins only. Materials for cultural and microscopic study are not obtainable, and, judging by experimental findings, even if the fluid in the anterior chamber were aspirated, it would likely be sterile when living organisms were present in the affected tissues. Systemic reactions are slight, cultures from the blood are negative, antibody production is minimal, and hence the usual agglutination reactions with suspected organisms are of little or no diagnostic value." With reference to his experimental work, he said: "Localization of the bacteria in the eye may sometimes be accidental and a part of other disease manifestations. However, the animal experiments, now amply corroborated, indicate clearly that localization and growth in most instances are due to peculiar, acquired or inherent, properties of the bacteria themselves and to their power to localize electively and that this is in part due to the production of a toxin or poison which affects specifically the tissues in which localization and growth occur. . . . Among the microörganisms isolated which manifested the greatest elective localizing power and with which the common forms of diseases of the eye have been reproduced, is a streptococcus which usually produces greenish or slightly hemolytic colonies on blood agar, which requires a reduced oxygen tension for its isolation, and from which autogenous therapeutic vaccines, of great value in many cases, have been prepared. . . . The experimental results indicate clearly that lesions in the eye which are associated with exudation, even though slight, are usually due to actual localization of microörganisms, while the milder manifestations may sometimes be due to absorption of toxins which are formed in the focus or elsewhere and reach the eye in the blood stream."

In 1932, Rosenow and Nickel[13] presented a statistical study of a large series of cases of experimental iritis in rabbits produced by the intravenous injection of streptococci obtained from human foci of infection. Two hundred and seventy-two rabbits were injected with freshly isolated streptococci obtained from foci of infection in 87 patients

with acute, chronic, primary or recurrent attacks of iritis, iridocyclitis and uveitis. Of these rabbits 41.6% developed eye lesions; 5% developed lesions in the joints. Ocular localization occurred in only 0.4% to 1.9% of rabbits injected with streptococci obtained from foci of infection in patients with miscellaneous diseases without lesions in the eyes. Of the rabbits injected with organisms obtained from patients with acute iritis 75% developed ocular lesions. In a series of 215 rabbits, it was found that organisms obtained from the tonsils localized in the eyes in 67%, organisms from the teeth in 53%, from the cervix in 50%, and from the prostate in 40%. Streptococci could be demonstrated in the tissues and could be recovered in cultures and these organisms again reproduced the lesion in other rabbits. However, they lost their specificity after 3 or 4 animal passages or subcultures. It was found that various strains of streptococci have characteristic cataphoretic velocities or electrical potentials which correspond closely to their specific localizing characteristics, so that it can be predicted from this test where the organisms will localize after intravenous injection. Rosenow has been able to produce hyperimmune sera in horses which give specific skin reactions and which can be used to produce immunity in patients harboring the specific strain of streptococcus.

More closely to reproduce experimentally the conditions found in man, Rosenow and Nickel infected the teeth of 7 dogs with four strains of streptococci obtained from patients with iritis. Three of these dogs developed a primary inflammatory reaction in the eyes, but recurrent inflammation did not occur during periods of observation of from 4 months to 3 years. In one dog, the teeth were infected on two separate occasions. Iritis developed after the second inoculation but not after the first. This result was interpreted as an indication that the eyes had become allergic to the streptococci.

The experiments carried out by these several workers seem to indicate clearly that inflammations of the uveal tract can be caused by direct bacterial metastasis to the eye, that certain strains of streptococci are more apt than others to cause ocular inflammations, and that the same strain of streptococcus at different times or growing under different conditions may have a greater or less tendency to localize in the eye. The fact remains, however, that these experiments do not furnish the complete answer to the problem of recurrent uveitis in man. The iritis and uveitis produced experimentally are not identical clinically or histologically with human iritis and uveitis, and it has not been possible to cause spontaneously recurrent inflammations of the eyes in animals even by the establishment of foci of infection in the teeth or elsewhere.

Because of these manifest defects in the experimental proof of repeated bacterial implantations in the eye as the explanation of recurrent human uveitis, A. L. Brown was attracted to the possibilities of the allergic theory of recurrent iritis and uveitis. Two methods of producing ocular anaphylaxis have been known for some time: 1, introducing foreign proteins, bacteria, or toxins into the eyeball and giving intravenous injections of the same substance after the sensitizing period, or 2, producing general sensitization by intravenous injection and then injecting the same material into the eye at a later period. A. L. Brown quotes a number of early experiments: In 1908, Nicole and Abt demonstrated the local sensitization of ocular tissues. They sensitized guinea

pigs by intraperitoneal injections of serum and produced ocular inflammation by injection of the same serum into the anterior chamber 32 days later. In 1910, Krusius produced general sensitization in guinea pigs by intraocular injection of cow serum. Also, he sensitized guinea pigs by subcutaneous injections and later produced ocular inflammation by anterior chamber injection of the same material. Kummel, in 1910, and Wessely, in 1911, sensitized one eye to foreign serum and then were able to produce ocular inflammations in the other eye by injections of the same serum. Woods, in 1916, sensitized animals by intraperitoneal injection of foreign protein and later perfused the heads with the same antigen and caused contraction of the pupils and small hemorrhages in the fundi. In 1919, Wibaut produced intraocular inflammation by injection of foreign protein into the vitreous 17 days after a preliminary injection of the same protein.

These various experiments demonstrated the possibility of producing allergic reactions in the eyes of animals. Considerable light was thrown upon the nature of these reactions by the studies of Derick,[5] Swift[15] and Andrews,[1] and of the Seegals.[14a,b] In 1926, the former authors demonstrated the occurrence of a secondary activation in about 50% of the skin reactions resulting from intradermal inoculation of certain strains of *Streptococcus viridans*. This secondary reaction occurred about 8 or 9 days after inoculation when the lesions had become sterile. It was considered to be allergic in type and was proved to be more similar to the tuberculin reaction than to the Arthus phenomenon. Later, these same authors were able to show that animals who showed secondary skin reactions had developed a general state of hypersensitiveness or allergy and that the eyes also had become allergic to the particular strain of streptococcus injected. Normal rabbits showed only a slight transient reaction if the cornea was scarified and a drop of bacterial sediment was rubbed into the cornea. In animals who had had a secondary skin reaction, similar inoculation of the cornea produced definite keratitis which persisted for from 2 to 15 days. This hypersensitive state could not be produced by primary intravenous injection of the streptococci. The establishment of an inflammatory focus seemed to be necessary to the production of the general and ocular allergy. The most marked reactions were obtained from foci in the skin, joints, and paranasal sinuses, but reactions were obtained also following injections into the subcutaneous tissues, muscles, peritoneal cavity, testicles, and vaginal mucosa. They demonstrated further that, ordinarily, streptococci of the viridans type injected intravenously disappear quickly from the blood stream without producing gross lesions. In some instances, however, especially when large doses are employed, the animals develop endocarditis or arthritis. These animals show hypersensitive rather than immune reactions on skin-test inoculations. Presumably, this holds true also for streptococci which have localized in the uveal tissues.

In 1931, the Seegals published their observations on ocular allergy. They found that: 1, rabbit eyes sensitized with guinea pigs' red blood cells or fresh egg white responded with an inflammatory reaction following the intravenous injection of the homologous but not of the heterologous antigen; 2, injection into the anterior chamber of 0.2 cc. of a multiple antigen containing ten separate ingredients is sufficient to

produce ocular hypersensitivity so that intravenous injection of 1 cc. of any one of the antigens will produce an inflammatory reaction in the sensitized eye. This hypersensitivity will persist for at least 8 months; 3, repeated daily intravenous injections of a single antigen fail usually to produce a reaction after the first few days. Injections of different antigens on succeeding days produce a continued sterile inflammatory process. Animals may develop minimal eye reactions following repeated intravenous injections of the same antigen if sufficient time is allowed to elapse between injections; and 4, unless massive doses of antigen are used to desensitize, permanent desensitization of the eye has not occurred in animals which have been followed for at least 8 months. The reaction is specific to the antigen originally used to sensitize the eye and does not depend on simple trauma to the eye. The Seegals demonstrated that a sterile inflammation may develop in the actively sensitized rabbit eye following the introduction of homologous antigen into the gastro-intestinal tract. Such reactions developed in 29% of 37 rabbits.

In 1932, A. L. Brown[3a,4] stated: "The ability of a toxin to sensitize local ocular tissues is significant in that it may be possible for a focus of organisms to eliminate some absorbable substance into the circulation and so sensitize the uveal tract that the recurrences of uveitis might represent periods of hypersensitiveness and the remissions periods of desensitization." He confirmed the findings of the Seegals that intraocular sensitization could be produced routinely only by the intraocular presence of the sensitizing medium. He found that guinea pig red blood cells or egg white produced typical ocular anaphylaxis when injected intravenously, provided the anterior chamber had been injected with the same material 10 days previously. The reaction did not occur if the first injection had been made under the conjunctiva and developed in lesser degree if the injection was made into the vitreous chamber.

Brown tested the ability of bacterial products to produce similar ocular allergy. He isolated a hemolytic streptococcus from an infected tooth root of a man with uveitis and injected a dilute suspension in sterile water into the anterior chambers of rabbits. Iritis developed within 14 to 48 hours and subsided in 5 to 6 days. On the tenth day, he injected 2 cc. of a heavy suspension of the same organism into an ear vein. Acute iritis developed in 8 to 10 hours but subsided in 24 to 30 hours. He obtained similar results with the use of toxin from the streptococcus of scarlet fever.

In 1934, A. L. Brown[3b,c] reported on a series of experiments designed to test the relative importance or frequency of direct metastatic focal infection and of ocular allergy in the production of iritis and uveitis. Using a strain of streptococcus known to produce iritis when injected into the carotid artery, foci of infection were implanted in parts remote from the eye. Ocular inflammation developed in one of 80 animals. When the eye had been sensitized previously by a toxic filtrate of the organism injected into the anterior chamber, the remote foci activated the eye in 25 of 30 rabbits. A similar strain of streptococcus was injected intravenously into 25 rabbits. Iritis developed in one of the 25. When the eye had been sensitized previously, iritis developed in 98 of 100 rabbits in which the streptococci were injected intravenously. In 1934, Traut obtained positive blood cultures in 5 patients with acute

iritis. However, Brown could get positive blood cultures in only 2 of 81 cases with active intraocular inflammation. One of these was in a patient with a septic abortion and the other in a patient with a blood-stream infection resulting from pyelitis. Brown cultured 37 specimens of aqueous from 27 cases of recurrent iridocyclitis, 5 sections of iris obtained by iridectomy, and the uveal tracts of 5 enucleated eyes. He was unable to recover any streptococci.

As a result of his studies, A. L. Brown concluded that the uveal inflammation produced by local bacterial sensitization is in most respects comparable to recurrent human uveal inflammation and that recurrent uveitis is probably due to the fact that the uveal tract is sensitized and activated repeatedly by a specific antigen.

To determine the efficacy of foreign protein therapy in the treatment of iritis and uveitis, A. L. Brown, 3d, studied the bactericidal properties of the aqueous and vitreous and the "interference" effect of parenteral administration of proteins on sensitization of the uveal tract. Cronstedt had found that the vitreous had essentially no bactericidal properties. Brown found that the aqueous was no more effective than the vitreous in inhibiting the growth of organisms. A suspension of organisms injected into the carotid artery usually produces panophthalmitis in the eye of the same side if the organism is sufficiently virulent. He was able to protect the eye against inflammation by the preliminary introduction of blood serum or preferably whole blood into the vitreous chamber. He also demonstrated that multiple ocular sensitization depends on the intraocular introduction of the antigens at the same time in practically equal quantities. Larger quantities of one protein, especially if administered first, clearly inhibit the sensitizing action of smaller quantities of another protein. In an animal generally immunized to typhoid vaccine to a relatively high serum titer, the eye could be sensitized by an average dose of bacterial antigen when the aqueous titer was 1 to 2, or even 1 to 18. With an aqueous titer of above 1 to 36, sensitization was not effected. If the typhoid antibodies were in the aqueous in a concentration of at least 1 to 78 before the introduction of the bacterial antigen, the ocular reaction failed to occur.

According to A. L. Brown, the blood titer in rabbits after typhoid immunization is 1 to 4000+. The aqueous titer is only 1 to 2. After puncture of the anterior chamber, the second aqueous has a titer of 1 to 18. After a second puncture, the titer of the third aqueous is 1 to 162. If three strips of surgical 10-day catgut, 10 mm. in length, soaked in typhoid vaccine were buried under the conjunctiva, the titer of the aqueous rose to 1 to 120 in 24 hours. After 8 days, the aqueous titer was 1 to 162. Brown has suggested, therefore, the advisability of puncturing the anterior chambers after the intravenous administration of typhoid vaccine in patients with resistant iritis or uveitis. The use of subconjunctival strips of catgut might also be permissible in certain cases.

MacLean[11] gave probable further support to the allergic theory of recurrent uveitis when he reported, in 1936, the production of iridocyclitis in both eyes of rabbits after local sensitization of only one eye. The inflammation developed less frequently in the untraumatized eye and was less pronounced when it occurred. Dutch rabbits were sen-

sitized by intravenous injection to a strain of *Streptococcus viridans* isolated from a patient with rheumatic fever. Scarification of the corneas and inoculation of a concentrated live broth culture of the streptococci proved that the corneas participated in the general sensitivity. Four months later, after the ocular reaction had entirely subsided, live broth cultures of the streptococci were injected intravenously. Thirty minutes after the injection, blood cultures were positive but aqueous cultures were negative. Within 24 to 48 hours, both eyes of all but one of the sensitized rabbits showed marked intraocular reactions. The keratitis was reactivated in all of the sensitized animals that had had the ophthalmic test previously. Reactions were obtained in 4 of 8 rabbits, even after the fourth intravenous injection. An agar focus was established under the skin of the back in the same rabbits one week later. An intraocular reaction developed in 2 of the rabbits.

Objections can be raised to the acceptance of the allergic mechanism demonstrated experimentally to produce iritis in animals as the mechanism of recurrent iritis and uveitis in man. The most potent objections are similar to those advanced against the theory of elective localization of bacteria. The intraocular inflammations are not identical, either clinically or histologically, with those seen in humans. The inflammations are more transitory and do not run the protracted course of many cases of human iritis and most cases of uveitis. Recurrence of the inflammation can be produced more readily by sensitization methods than by direct intravenous injections of specific bacteria. But the recurrences tend to be increasingly milder and more transient rather than more severe and resistant as they are in many clinical cases.

Alan Woods,[16] in the section on "Immunology" in Berens' "The Eye and Its Diseases," states: "Kolmer[9] and others have suggested that many inflammatory diseases of the eye—keratitis, iritis, and uveitis—which clinically appear to be related to foci of infection, in many instances may be due to allergy and not to bacterial metastasis. The grounds advanced for such reasoning are the usual inability to culture bacteria from the inflamed eye or its humors, and the flare-ups in the inflammatory ocular picture which often follow the administration of a vaccine obtained from the primary focus of infection." After discussing the necessity of proving 1, that patients with uveitis and other forms of ocular disease have a higher degree of sensitivity than normal individuals to bacteria isolated from foci of infection, and 2, that clinical improvement follows desensitization with the bacterial products, Woods concludes: "It is therefore evident that while experimental evidence indicates that certain eye lesions from a focus of infection may be due to an allergic mechanism rather than to bacterial metastasis, clinical proof of such an allergic mechanism is lacking, and must of necessity be difficult to produce." It seems possible that the "elective localizing" character of the streptococci concerned in these diseases may account at least for the local ocular hypersensitiveness exhibited by patients with recurrent uveitis. Recently, Rosenow has noted specific skin reactions in humans to hyperimmune sera produced in horses by repeated injections of specific strains of streptococci. This finding suggests that individuals suffering from recurrent iridocyclitis or uveitis may be hypersensitive or allergic to the products of a strep-

tococcus with specific affinity for the uveal tract. The attacks of uveitis may occur then only at those times when the streptococci in the focus of infection develop this specific affinity.

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